Antifungallerdeki Yenilikler
Kombinasyon Yapalım mı?

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İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

Fungal İnfeksiyonlar

Campitelli M. J Clin Med Res 2017;9:451-6

Antifungal Kombinasyon

- Additif Etki
- Sinerji
- Antagonizma

İn vitro ve İn vivo Antifungal Etkileşimleri

Tür/Kombinasyon	Genel in vitro patern	Genel in vivo patern
Cryptococcus neoformans		
AmB + Flusitozin	Fark yok, Antagonizma, Sinerji	Daha iyi survi, daha kötü survi, doku yükünde azalma
Azol + Flusitozin	Fark yok, Sinerji	Daha iyi survi, daha kötü survi, doku yükünde azalma
AmB + Azol	Fark yok	Daha iyi survi, daha kötü survi, doku yükünde azalma
Ekinokandin + AmB	Sinerji	Veri yok
Ekinokandin + Azol	Fark yok	Veri yok

Day JN. N Engl J Med 2013;368:1291-1302
Campitelli M. J Clin Med Res 2017;9:451-6
Antimicrob Agents Chemother 2004; 48: 693–715.
Clin Microbiol Infect 2008; 14 (Suppl. 4): 65–70

İn vitro ve İn vivo Antifungal Etkileşimleri

Tür/Kombinasyon	Genel in vitro patern	Genel in vivo patern
Candida spp.		
AmB + Flusitozin	Sinerji, Fark yok	Daha iyi survi, doku yükünde azalma
Azol + Flusitozin	Sinerji, Fark yok, Antagonizma	Daha iyi survi, doku yükünde azalma
AmB + Azol	Antagonizma	Daha iyi, aynı, daha kötü survi, doku yükünde azalma ya da değişiklik olmaması
Ekinokandin + AmB	Fark yok	Doku yükünde azalma ya da değişiklik olmaması

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İn vitro ve İn vivo Antifungal Etkileşimleri

Tür/Kombinasyon	Genel in vitro patern	Genel in vivo patern
Aspergillus spp.		
AmB		
AmB		ünde
Ekinokandin + AmB	Sinerji, Fark yok	Daha iyi survi, doku yükünde azalma ya da değişiklik olmaması
Ekinokandin + Azol	Sinerji, Fark yok	Daha iyi survi, doku yükünde değişiklik olmaması

Kriptokok İnfeksiyonlarında AmB + flusitozin – Mortaliteyi azaltıyor
Diğer invaziv fungal infeksiyonlar için literatürde kombinasyon tedavisinin yeterliliği, ne zaman verileceği ve riskleri konusunda kanıt düzeyi yüksek kontrollü çalışma yok

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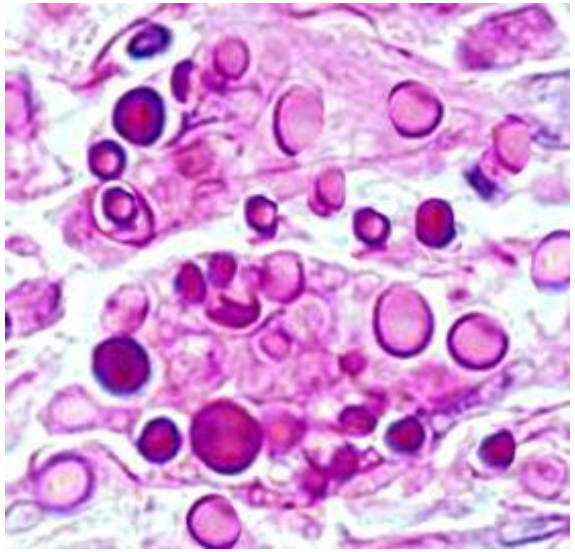
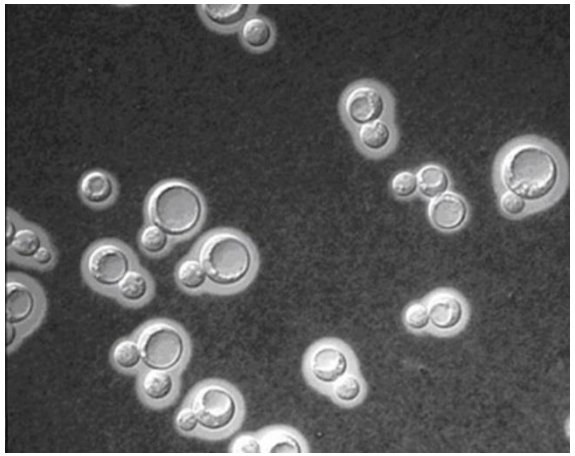
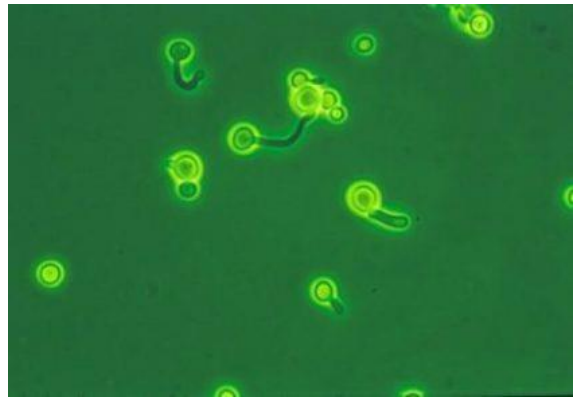
Clin Microbiol Infect 2008; 14 (Suppl. 4): 65–70

Sinerji ve Antagonizma Mekanizmaları

Antifungal Kombinasyon	Sinerji veya Antagonizma	Mekanizma	Mikroorganizma
Terbinafin + Azol	S	Ergosterol sentezinin inhibisyonu	*C. albicans* *C. neoformans* *C. glabrata*
AmB veya Azol + Flusitozin	S	AmB veya azolle hücre duvarında hasar ile flusitozinin hücre içine girişi	Pulmoner kriptokok infeksiyonu Kandida sepsisi
AmB + Azol	A	Fungal hücrede hedef modifikasyonu	İnvaziv kandidiyazis
AmB + Flusitozin	A	Hücre membran fonksiyonunda değişiklik	*C. neoformans* ve *C. tropicalis*



Kriptokok İnfeksiyonları

Kriptokok İnfeksiyonları

- İlk kombinasyon fikri 40 yıldan daha önce ortaya çıktı – Başarıyla tedavi edilen iki vakanın yayımlanması

Postgraduate Medical Journal (May 1976) **52,** 305–308.

Combination antifungal therapy for cryptococcal meningitis

J. S. TOBIAS*
M.R.C.P.

P. F. M. WRIGLEY*
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Summary

Two patients with Hodgkin's disease and cryptococcal meningitis are described. Both patients were treated with a combination of the two antifungal agents, amphotericin B and flucytosine. Nephrotoxicity was easily reversible in both patients and clinical improvement was seen with this combination therapy. Intrathecal therapy with amphotericin B was used in both patients. The optimal treatment of this disease may prove to be a combination of oral flucytosine, with amphotericin B given by intrathecal injection as well as rapid low dose intravenous injection.

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ORIGINAL ARTICLE FREE PREVIEW ARCHIVE

A Comparison of Amphotericin B Alone and Combined with Flucytosine in the Treatment of Cryptoccal Meningitis

John E. Bennett, M.D., William E. Dismukes, M.D., Richard J. Duma, M.D., Gerald Medoff, M.D., Merle A. Sande, M.D., Harry Gallis, M.D., John Leonard, M.D., Branch T. Fields, M.D., Major Bradshaw, M.D., Hubert Haywood, M.D., Zell A. McGee, M.D., Thomas R. Cate, M.D., et al.

July 19, 1979
N Engl I Med 1979; 301:126-131

Amfoterisin B
10 hafta

51 Epizod

Amfoterisin B + flusitozin
6 hafta

Bennett JE. N Engl J Med 1979;30:126-31

OPEN ACCESS Freely available online

PLoS one

Major Role for Amphotericin B–Flucytosine Combination in Severe Cryptococcosis

Françoise Dromer[1]*, Claire Bernede-Bauduin[2,3], Didier Guillemot[2,3,4], Olivier Lortholary[1,5] for the French Cryptococcosis Study Group

- 208 olgu
- 2. hafta ve 3. ay tedavi yetersizliği (fungal ya da mortalite)
- 2. haftada tedavi yetersizliği
  - AmB + flusitozin grubu %26
  - Diğer gruplar %56

P<0.001

Dromer F. PLoSONE 2008; 3(8): e2870. doi:10.1371/journal.pone.0002870

Medical Mycology June 2008, **46**, 393–395

informa
healthcare

Fluconazole alone or combined with flucytosine for the treatment of AIDS-associated cryptococcal meningitis

ERIC MILEFCHIK*, MARY ANN LEAL*, RICHARD HAUBRICH†, SAMUEL A. BOZZETTE†, JEREMIAH G. TILLES‡, JOHN M. LEEDOM*, J. ALLEN MCCUTCHAN† & ROBERT A. LARSEN*

**University of Southern California, †University of California, San Diego, and ‡University of California, Irvine, California, USA*

- Prospektif Faz 2
- Flukonazol 800 -2000 mg vs Flukonazol 800 -2000 mg + flusitozin

Medical Mycology June 2008, **46**, 393–395

informa
healthcare

Fluconazole alone or combined with flucytosine for the treatment of AIDS-associated cryptococcal meningitis

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**University of Southern California, †University of California, San Diego, and ‡University of California, Irvine, California, USA*

	Fluconazole alone				Fluconazole plus flucytosine			
Dose (mg/kg·day)	800	1200	1600	2000	800	1200	1600	2000
Number of patients	9	16	16	8	8	8	16	8
Male	100%	94%	94%	100%	100%	100%	100%	100%
Median age	35	40	35	36	38	34	37	37
Median CD4 cells	8	36	33	35	25	29	11	47
Median CSF CrAg	1:1024	1:128	1:64	1:32	1:512	1:64	1:512	1:256
Minimum CrAg	1:2	Neg.	Neg.	Undil.	1:2	Neg.	1:2	1:2
Maximum CrAg	1:8192	1:65536	1:8192	1:4096	1:131072	1:32768	1:32768	1:8192
1st O.I.	56%	25%	44%	88%	38%	62%	44%	25%
Overall success	11%	37%	62%	62%	75%	87%	62%	75%

CD4 cells, CD4+ T lymphocytes count. Min. CrAg., Minimum CSF cryptococcal latex agglutination antigen titer. Max. CrAg., Maximum CSF cryptococcal latex agglutination antigen titer. Neg. Negative. Undil., Undilute. 1st O.I., first opportunistic infection. Success, clinical and microbiological, i.e., alive and CSF culture negative on or before week 10.

A Phase II Randomized Trial of Amphotericin B Alone or Combined with Fluconazole in the Treatment of HIV-Associated Cryptococcal Meningitis

Peter G. Pappas,[1] Ploenchan Chetchotisakd,[8] Robert A. Larsen,[2] Weerawat Manosuthi,[9] Michele I. Morris,[4] Thomansak Anekthananon,[10] Somnuek Sungkanuparph,[11] Khauncahi Supparatpinyo,[12] Tracy L. Nolen,[5] Louise O. Zimmer,[5] Amy S. Kendrick,[5] Phillip Johnson,[6] Jack D. Sobel,[7] and Scott G. Filler[3]

- 143 hasta – 3 grup 14 gün
  - AmB
  - AmB + flukonazol 400 mg – sonrasında flukonazol
  - AmB + flukonazol 800 mg - sonrasında flukonazol

Yüksek doz flukonazol + AmB daha etkin ve iyi tolere edilmekte

Clinical Infectious Diseases 2009; 48:1775–83

Published in final edited form as:
Clin Infect Dis. 2010 February 1; 50(3): 338–344. doi:10.1086/649861.

Combination flucytosine and high dose fluconazole is superior to fluconazole monotherapy for cryptococcal meningitis: a randomized trial in Malawi

JC Nussbaum[1,2,*], A Jackson[1,*], D Namarika[1,3], J Phulusa[1], J Kenala[1], C Kanyemba[1], JN Jarvis[4,5,6], S Jaffar[7], MC Hosseinipour[1,8], D Kamwendo[1], CM van der Horst[8], and TS Harrison[4]

- Randomize çalışma
- Flukonazol 1200 mg/gün vs + flusitozin 2 hafta, flukonazol 800 mg/gün 10 hafta
- 41 olgu
- Kombinasyon tedavisi daha fungisidal ($p<0.001$)
- Kombinasyon tedavisinde 2. hafta ölüm oranı daha düşük
  - 2 hafta %10 vs %37 HR 0.24
  - 10 hafta %43 vs %58 HR 0.59

Journal of Infection (2012) 64, 76–81

ELSEVIER

BIAMM British Infection Association

www.elsevierhealth.com/journals/jinf

Short course amphotericin B with high dose fluconazole for HIV-associated cryptococcal meningitis

Conrad K. Muzoora [a,*], Ta
John Ssentamu [a], Pasco H
Joseph N. Jarvis [b], Shabb

İkinci haftada infeksiyon klirensi kombinasyon tedavisi alan grupta daha iyi ($p < 0.001$)

- 30 HIV pozi
- 1200 mg flu en 800 mg flukonazol/
- Daha önce aynı merkezde flukonazolle tedavi edilen 60 hasta ile karşılaştırma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

Jeremy N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D.,

- Randomize kontrollü
- AmB + Flusitozin vs AmB + yüksek doz flukonazol
- 14 ve 70 gün survi
- 299 olgu

Day J. N Engl J Med 2013;368:1291-1302

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

Jeremy N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D.,

Table 2. Primary and Key Secondary Outcomes.*

Outcome	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)
Coprimary outcomes			
Death by day 14			
No. of deaths	25	15	20
Death by day 182¶			
No. of deaths	53	34	45
Probability of survival (95% CI)	0.46 (0.37 to 0.57)	0.65 (0.56 to 0.75)	0.54 (0.45 to 0.65)
Estimated change in CSF fungal count in first 14 days (95% CI) — $\log_{10}$ CFU/ml/day	−0.31 (−0.34 to −0.29)	−0.42 (−0.44 to −0.40)	−0.32 (−0.34 to −0.29)
CSF fungal clearance			
No. of patients with documented clearance	52	74	63
Clearance rate per person-wk of follow-up (95% CI)	0.17 (0.13 to 0.23)	0.39 (0.31 to 0.50)	0.26 (0.20 to 0.34)

AmB + flusitozin - survi daha iyi (p=0.04)
AmB + flukonazol – survide fark yok (p=0.42)

Day J. N Engl J Med 2013;368:1291-13

Eur J Clin Microbiol Infect Dis (2014) 33:1339–1344
DOI 10.1007/s10096-014-2074-2

ARTICLE

Comparison of flucytosine and fluconazole combined with amphotericin B for the treatment of HIV-associated cryptococcal meningitis: a systematic review and meta-analysis

Z.-W. Yao · X. Lu · C. Shen · D.-F. Lin

- Primer sonlanım 14 ve 70 günlerde mortalite
- Sekonder sonlanım erken fungisidal aktivite
- Randomize kontrollü ve prospektif çalışmalar

Eur J Clin Microbiol Infect Dis (2014) 33:1339–1344
DOI 10.1007/s10096-014-2074-2

ARTICLE

Comparison of flucytosine and fluconazole combined with amphotericin B for the treatment of HIV-associated cryptococcal meningitis: a systematic review and meta-analysis

Z.-W. Yao · X. Lu · C. Shen · D.-F. Lin

- Flusitozin grubunda 2. hafta mortalitesi daha düşük %44 [RR 0.56, %95 GA 0.33–0.95, p=0.03]
- Erken fungisidal aktivite Flusitozin AmB grubunda daha kısa (p<0.00001]
- Gruplar arasında 3. ay mortalitesinde fark yok (p= 0.15)
- Gruplar karşılaştırıldığında istenmeyen etkiler benzer sıklıkta

Rehberler Ne Öneriyor?

HIV İnfeksiyonu + Kriptokokal Meningoensefalit

IDSA GUIDELINES

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

John R. Perfect,[1] William E. Dismukes,[2] Francoise Dromer,[3] David L. Goldman,[4] John R. Graybill,[5] Richard J. Hamill,[6] Thomas S. Harrison,[7] Robert A. Larsen,[8] Olivier Lortholary,[9,10] Minh-Hong Nguyen,[4] Peter G. Pappas,[2] William G. Powderly,[11] Nina Singh,[12] Jack D. Sobel,[13] and Tania C. Sorrell[14]

Rejim	Süre	Kanıt Düzeyi
İndüksiyon		
AmBd (0.7–1.0 mg/kg/g) + flusitozin (100 mg/kg/g)	2 hafta	AI
Lipozomal AmB (3–4 mg/kg/g) veya ABLC (5 mg/kg/g, renal fonksiyonlarla ilgili endişe varsa) + flusitozin (100 mg/kg/g)	2 hafta	BII
İndüksiyon tedavi alternatifleri		
AmBd + flukonazol		BI
Flukonazol + flusitozin		BII

SOT + Kriptokokal Meningoensefalit

Rejim	Süre	Kanıt Düzeyi
İndüksiyon		
Lipozomal AmB (3–4 mg/kg/g) veya ABLC (5 mg/kg/g, renal fonksiyonlarla ilgili endişe varsa) + flusitozin (100 mg/kg/g)	2 hafta	BIII

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HIV İnfeksiyonu yok, SOT yok+ Kriptokokal Meningoensefalit

Rejim	Süre	Kanıt Düzeyi
İndüksiyon		
AmBd (0.7–1.0 mg/kg/g) + flusitozin (100 mg/kg/g)	2*- ≥ 4 hafta**	BII
Lipozomal AmB (3–4 mg/kg/g) veya ABLC (5 mg/kg/g) + flusitozin (100 mg/kg/g)	≥ 4 hafta**	BIII

**Four weeks are reserved for patients with meningitis who have no neurological complications, who have no significant underlying diseases or immunosuppression, and for whom the cerebrospinal fluid culture performed at the end of 2 weeks of treatment does not yield viable yeasts; during the second 2 weeks, lipid formulations of AmB may be substituted for AmBd.
Fluconazole is given at 200 mg per day to prevent relapse after induction therapy, and consolidation therapy is recommended.
*For patients who have a low risk of therapeutic failure. Low risk is defined as an early diagnosis by history, no uncontrolled underlying condition or severe immunocompromised state, and an excellent clinical response to initial 2-week antifungal combination course

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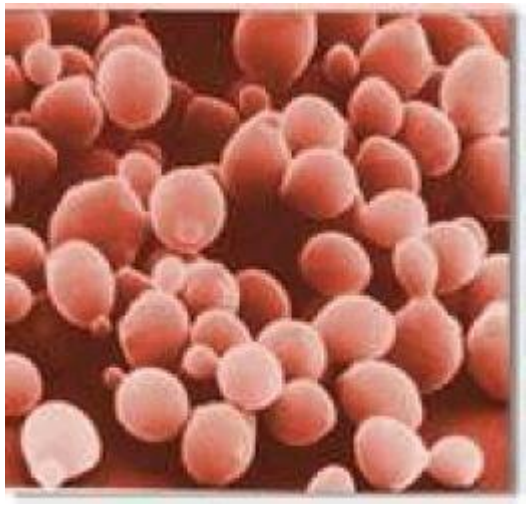
İstenmeyen Etki

- AmB’nin glomeruler filtrasyon hızında azalmaya yol açması
- Flusitozin eliminasyonunun azalması
- Antimikotik aktivitede artış ancak immünsupresif ve hepatotoksik etkide de artış olması

Francis P. Clin Infect Dis 1992;15:1003-8
Vermes A. J Antimicrob Chemother 2000;46:171-9

Kandida İnfeksiyonları



REVIEW

Virulence 6:4, 362–371; May/June 2015; © 2015 Taylor and Francis Group, LLC

Synergistic combinations of antifungals and anti-virulence agents to fight against *Candida albicans*

Jinhui Cui[1,#], Biao Ren[1,2,#], Yaojun Tong[1,3], Huanqin Dai[1,*], and Lixin Zhang[1,*]

[1]CAS Key Laboratory of Pathogenic Microbiology and Immunology; Institute of Microbiology; Chinese Academy of Sciences; Beijing, China; [2]State Key Laboratory of Oral Diseases; West China Hospital of Stomatology; Sichuan University; Chengdu, China; [3]Novo Nordisk Foundation Center for Biosustainability; Technical University of Denmark; Hørsholm, Denmark

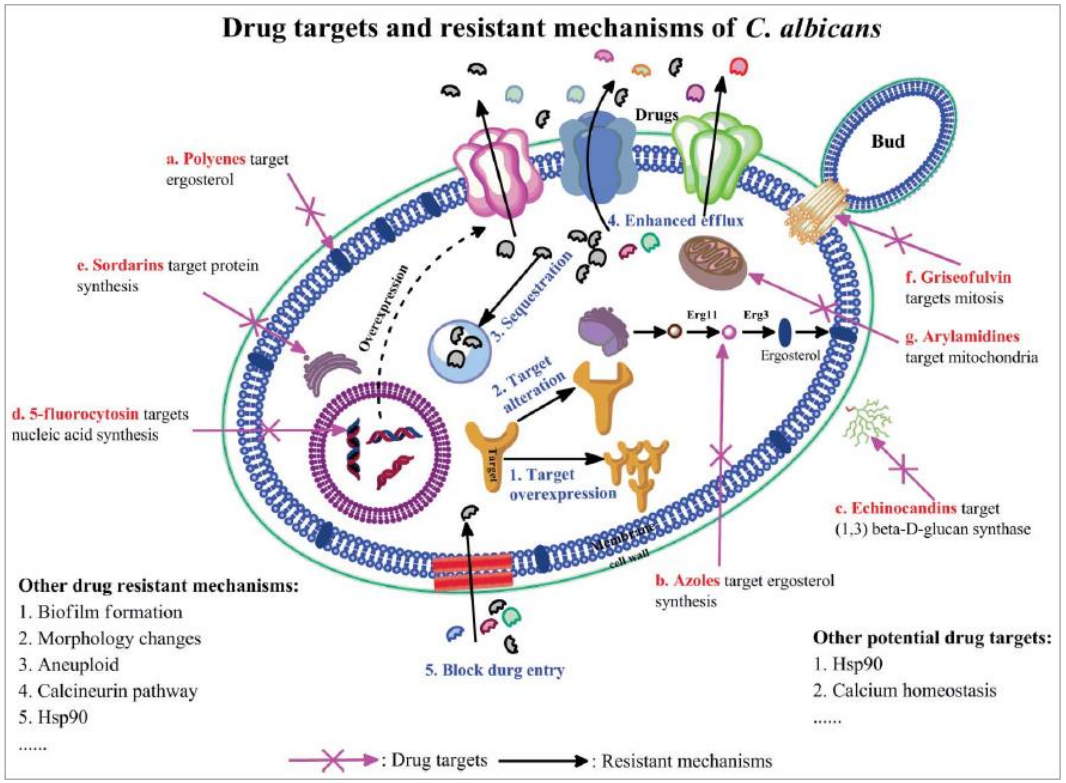
Table 1. *Selected synergistic combinations against *C. albicans in vitro* and *in vivo*.

Data from	Wild type or resistance#	Synergistic combination	Reference
In vitro Animal	Wild type and Resistance	Beauvericin + Clotrimazole, or Fluconazole, or Itraconazole, or Ketoconazole, or Miconazole	Unpublished
In vitro	Wild type and Resistance	Rapamycin + peptides	Unpublished
In vitro	Wild type and Resistance	Ketoconazole + Avilamycin	Unpublished
In vitro	Wild type and Resistance	Ketoconazole + Spinosad	Unpublished
In vitro	Wild type and Resistance	Nitroimidazoles + Amphotericin B	83
In vitro	Wild type and Resistance	Histatin 5 and its analogs Amphotericin B	84
In vitro	Wild type and Resistance	Tetrandrine + Ketoconazole	85
In vitro	Wild type and Resistance	Fluconazole + Thymol, or Carvacrol	86
In vitro	Wild type and Resistance	Geldanamycin + Fluconazole	87
In vitro	Wild type and Resistance	Pure polyphenol curcumin I + Fluconazole, or Miconazole, or Ketoconazole, or Itraconazole, or Voriconazole, or Nystatin or Amphotericin B	88
In vitro	Wild type and Resistance	Berberine + Fluconazole	89-91
In vitro	Wild type and Resistance	Fluconazole + alverine citrate, or Caspofungin, Latrunculin-A, or Wortmannin, or Fenpropimorph	92
In vitro	Wild type and Resistance	Tunicamycin + FK506, or Cyclosporine-A	92
In vitro	Wild type and Resistance	Wortmannin + Tunicamycin, or FK506	92
In vitro	Wild type and Resistance	Posaconazole + Caspofungin, or FK506	93
In vitro	Wild type and resistance	Amphotericin B + Terbinafine	94
In vitro	Wild type and Resistance	Flucytosine + Econazole, or Miconazole	95
In vitro	Wild type and Resistance	Fluvastatin + Fluconazole, or Itraconazole	96
In vitro	Wild type and Resistance	FK506 + Fluconazole, or Voriconazole, or Itraconazole	97
In vitro	Wild type and Resistance	Retigeric acid B + Fluconazole, or Ketoconazole, or Itraconazole	98
In vitro	Wild type and Resistance	Lactoferrin + Fluconazole, or Itraconazole	99
In vitro	Wild type and Resistance	Farnesol + Fluconazole, or Ketoconazole, or Miconazole, or Amphotericin B	100
In vitro	Wild type and Resistance	Amiodarone + Fluconazole, or Voriconazole, or Itraconazole	101
In vitro	Resistance	Eugenol + Amphotericin B, or Fluconazole	102
In vitro	Resistance	Honokiol + Fluconazole	103
In vitro	Resistance	Glabridin + Fluconazole	104
In vitro	Resistance	Tioconazole + Butylated hydroxyanisole	105
In vitro	Resistance	Baicalein + Amphotericin B	106
In vitro	Resistance	Curcumin+ R6G, or Ketoconazole, or Itraconazole, or Miconazole	107
In vitro	Resistance	Anidulafungin + Posaconazole, or Amphotericin B	108
In vitro	Resistance	Caspofungin + Posaconazole, or Micafungin	108
In vitro	Resistance	Minocycline + Fluconazole	109
In vitro	Resistance	Baicalein + Fluconazole	110

In vitro	Resistance	Baicalein + Fluconazole	110
In vitro	Resistance	Ofloxacin + Fluconazole	111
In vitro	Biofilm and Planktonic cells	Fluconazole + FK506, or Cyclosporine A	112
In vitro	Biofilm and Planktonic cells	Berberine + Miconazole	113
In vitro	Biofilm and Planktonic cells	Aspirin + Amphotericin B	114
In vitro	Biofilm	Tyrocidines + Amphotericin B, or Caspofungin	115
In vitro	Biofilm	Amphotericin B + Drospirenone, or Perhexiline, or Toremifene	116
In vitro	Biofilm	Caspofungin + Drospirenone, or Perhexiline, or Toremifene	116
In vitro	Biofilm	Amphotericin B + N-acetylcysteine, or EDTA, or Ethanol, or Talactoferrin	117
In vitro	Biofilm	Fluconazole + N-acetylcysteine, or EDTA, or Ethanol, or Talactoferrin	117
In vitro	Biofilm	Terpenes + Fluconazole	118
In vitro	Biofilm	Doxycycline + Fluconazole	119
In vitro	Biofilm	Silver nanoparticles + nystatin, or chlorhexidine digluconate	120
In vitro	Biofilm	Doxycycline + Fluconazole	121
In vitro	Biofilm	Shearinines D (3) and E (4) + Amphotericin B	122
In vitro	Biofilm	Verapamil + Fluconazole, or Tunicamycin	123
In vitro	Biofilm	Cyclosporine A + Fluconazole, or Voriconazole, or Amphotericin B, or Caspofungin	124
In vitro	Biofilm	Amphotericin B + Rifampicin, or Clarithromycin	125
Animal	Wild type and resistance	Posaconazole + Caspofungin, or FK506	126
Animal	Resistance	Amphotericin B + Caspofungin	127
Animal	Resistance	Tetrandrine + Ketoconazole	128
Animal	Wild type	Berberine + Amphotericin B	129
Animal	Wild type	Cilofungin + Amphotericin B	130
Animal	Wild type	Antimicrobial peptides + Caspofungin	131
Animal	Wild type	Nikkomycin Z + R 3783	132
Animal	Wild type	Amphotericin B + Ketoconazole, or 5-Fluorocytosine	133
Animal	Wild type	5-Fluorocytosine + Fluconazole, or Itraconazole	133

Table 1. *Selected synergistic combinations against *C. albicans in vitro* and *in vivo*. *(Continued)*

Data from	Wild type or resistance#	Synergistic combination	Reference
Animal	Biofilm	Fluconazole + FK506, or Cyclosporine A	112
Clinic trials	Clinical	Amphotericin B + 5-Fluorocytosine	134-137
Clinic trials	Clinical	5-Fluorocytosine + Azoles	138
Clinic trials	Clinical	Amphotericin B + Azoles	139
Clinic trials	Clinical	Terbinafine + Itraconazole or Fluconazole	140
Clinic trials	Clinical	Mycograb + lipid-associated amphotericin B	141



Infection. 1996 Nov-Dec;24(6):426-32.

A randomized study comparing fluconazole with amphotericin B/5-flucytosine for the treatment of systemic Candida infections in intensive care patients.

Abele-Horn M[1], Kopp A, Sternberg U, Ohly A, Dauber A, Russwurm W, Büchinger W, Nagengast O, Emmerling P.

- Prospektif randomize
- Flukonazol vs AmB + flusitozin
- 72 non-nötropenik sistemik *Candida* infeksiyonu olgusu
- Pnömoni ve sepsis – klinik gidişte fark yok
- Peritonit - %25 vs %55
  - Patojen eradikasyonu %50 vs %86

Candida İnfeksiyonları – AmB + Azoller

- Antagonist olabilir

Drugs 2005;65:1461-80

- Etki değişmez

Antimicrob Agents Chemother 2003;47:3657-59

- Additif olabilir

Clin Infect Dis 2003;36:1221-8

A Randomized and Blinded Multicenter Trial of High-Dose Fluconazole plus Placebo versus Fluconazole plus Amphotericin B as Therapy for Candidemia and Its Consequences in Nonneutropenic Subjects

John H. Rex, Peter G. Pappas, Adolf W. Karchmer, Jack Sobel, John E. Edwards, Susan Hadley, Corstiaan Brass, Jose A. Vazquez, Stanley W. Chapman, Harold W. Horowitz, Marcus Zervos, David McKinsey, Jeannette Lee, Timothy Babinchak, Robert W. Bradsher, John D. Cleary, David M. Cohen, Larry Danziger, Mitchell Goldman, Jesse Goodman, Eileen Hilton, Newton E. Hyslop, Daniel H. Kett, Jon Lutz, Robert H. Rubin, W. Michael Scheld, Mindy Schuster, Bryan Simmons, David K. Stein, Ronald G. Washburn, Linda Mautner, Teng-Chiao Chu, Helene Panzer, Rebecca B. Rosenstein, and Jenia Booth, for the National Institute of Allergy and Infectious Diseases Mycoses Study Group*

- Toplam 219 hasta

Table 3. Distribution of infecting *Candida* species and analysis of causes of failure for infection to respond to therapy.

Variable	*Candida albicans*		*Candida glabrata*		*Candida parapsilosis*		*Candida tropicalis*		*Candida lusitaniae*		*Candida kefyr*		Total	
										group	FP group	FA group	FP group	FA group
No. of subjects											0	1	107	112
No. of subjects whose infection to respond to therapy														
Blood cultures did not clear										—	—	—	18	7
Early withdrawal from therap											—	—	11	9
Drug-related toxicity										—	—	—	10	9
Other causes	3[a]	4	2[a]	—	—	—	—	1	—	—	—	—	4	5
No. of subjects who experienced relapse														
Recurrent candidemia	1	—	2[b]	1[d]	1[b]	—	—	1[d]	—	—	—	—	3	1
Use of antifungal therapy	1	2	—	2	—	—	—	—	—	—	—	—	1	4
Total no. (%) of infections that failed to respond to therapy	35 (51)	23 (34)	9 (41)	9 (50)	3 (23)	3 (19)	3 (43)	3 (23)	—	1 (50)	—	—	47 (44)	35 (31)

Kombinasyon grubunda fungemi klirensi daha yüksek oranda ve daha hızlı

NOTE. Values shown in the first row are numbers of subjects with ⩾1 blood culture positive for a given species. The distribution of species did not differ between treatment groups ($P > .5$, by χ^2 test). [illegible] cases of fungemia involving mixed pathogens in the fluconazole plus placebo (FP) treatment arm involved *C. albicans* and *C. glabrata* (3 subjects) and *C. glabrata* and *C. parapsilosis* (1 patient). In the fluconazole plus am[illegible]tericin B deoxycholate (FA) treatment arm, they involved *C. albicans* and *C. glabrata* (1 patient), *C. albicans* and *C. parapsilosis* (2 subjects), *C. albicans* and *C. tropicalis* (1 patient), *C. glabrata* and *C. parapsilosis* (1 patient), and *C. glabrata* and *C. tropicalis* (1 patient). The comparisons between study regimens are not significant for any individual species. However, the comparison of failure to clear the bloodstream is significant for a[illegible] species taken together ($P = .02$).

A Randomized and Blinded Multicenter Trial of High-Dose Fluconazole plus Placebo versus Fluconazole plus Amphotericin B as Therapy for Candidemia and Its Consequences in Nonneutropenic Subjects

John H. Rex, Peter G. Pappas, Adolf W. Karchmer, Jack Sobel, John E. Edwards, Susan Hadley, Corstiaan Brass, Jose A. Vazquez, Stanley W. Chapman, Harold W. Horowitz, Marcus Zervos, David McKinsey, Jeannette Lee, Timothy Babinchak, Robert W. Bradsher, John D. Cleary, David M. Cohen, Larry Danziger, Mitchell Goldman, Jesse Goodman, Eileen Hilton, Newton E. Hyslop, Daniel H. Kett, Jon Lutz, Robert H. Rubin, W. Michael Scheld, Mindy Schuster, Bryan Simmons, David K. Stein, Ronald G. Washburn, Linda Mautner, Teng-Chiao Chu, Helene Panzer, Rebecca B. Rosenstein, and Jenia Booth, for the National Institute of Allergy and Infectious Diseases Mycoses Study Group[a]

- Fluko … n)
- 30. g…
- Gene…
- Kan kültür negatifliği sağlanamaması %17 vs %6 (p=0.02)

Kombinasyon daha başarılı ve daha yüksek oranda klirens sağlıyor

Candida İnfeksiyonları – Ekinokandin + Azol

- Klinik çalışma rapor edilmemiş
- Posakonazol + kaspofungin veya mikafungin
  - İn vitro ve hayvan deneylerinde
- Posakonazol + kaspofungin
  - İn vitro ve in vivo ekinokandin dirençli *C. albicans* izolatları da dahil sinerjik

PLoS One 2013;8:e57672

- *C. albicans, C. glabrata, C. parapsilosis*
  - Azol ya da ekinokandine dirençli izolatlar – kombinasyona duyarlı olabilir
  - Posakonazol + ekinokandin kombinasyonunda antagonistik etki saptanmamış

Antimicrob Agents Chemother 2011;55:1543-8

Candida İnfeksiyonları – Ekinokandin + Azol Vaka Raporları

BMC Infectious Diseases

BioMed Central

Case report

Open Access

Successful treatment of *Candida parapsilosis* mural endocarditis with combined caspofungin and voriconazole

Víctor López-Ciudad*[1], María J Castro-Orjales[1], Cristóbal León[2], César Sanz-Rodríguez[3], María J de la Torre-Fernández[1], Miguel A Pérez de Juan-Romero[4], María D Collell-Llach[4] and María D Díaz-López[5]

Eur J Clin Microbiol Infect Dis (2005) 24: 753–755
DOI 10.1007/s10096-005-0038-2

CONCISE ARTICLE

D. C. B. Lye · A. Hughes · D. O'Brien · E. Athan

Candida glabrata prosthetic valve endocarditis treated successfully with fluconazole plus caspofungin without surgery: a case report and literature review

[redacted] CASE REPORTS

Micafungin plus Fluconazole in an Infected Knee with Retained Hardware due to *Candida albicans*

Christopher M Bland and Sanil Thomas

Rehberler Ne Öneriyor?

Clinical Infectious Diseases

IDSA GUIDELINE

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

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

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

- SSS *Candida* infeksiyonu
- Doğal kapak endokarditi
- Flukonazol dirençli *Candida* endoftalmiti

SSS *Candida* İnfeksiyonu

İndüksiyon Tedavisi

Lipozomal AmB, 5 mg/kg/g, ± oral flusitozin, 25 mg/kg 4 x 1,

(güçlü öneri; düşük kanıt düzeyi)

Candida Endokarditi

Lipozomal AmB 3–5mg/kg/g, ±, flusitozin25 mg/kg 4 x 1 veya
Yüksek doz ekinokandin (kaspofungin 150 mg/g,
mikafungin 150 mg/g, veya anidulafungin 200 mg/g)
(güçlü öneri; düşük kanıt düzeyi)

Endoftalmit

Flukonazol/vorikonazol dirençli izolatlar

Lipozomal AmB, 3–5 mg/kg /g, ± oral flusitozin, 25 mg/kg 4 x 1 (güçlü öneri; düşük kanıt düzeyi)

Maküler tutulum varsa yukarıdakilere ek olarak intravitreal enjeksiyon

AmBd, 5–10 µg/0.1 mL steril su içinde, veya

Vorikonazol, 100 µg/0.1 mL steril su ya da salin içinde (güçlü öneri; düşük kanıt düzeyi)

GUIDELINE ARTICLE

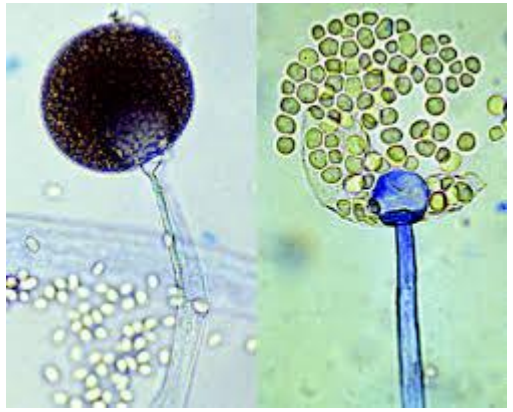
ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Samir Agrawal,[2] Livio Pagano,[3] Georgios Petrikkos,[4] Andreas H. Groll,[5] Anna Skiada,[6] Cornelia Lass-Flörl,[7] Thierry Calandra,[1] Claudio Viscoli[8] and Raoul Herbrecht[9]

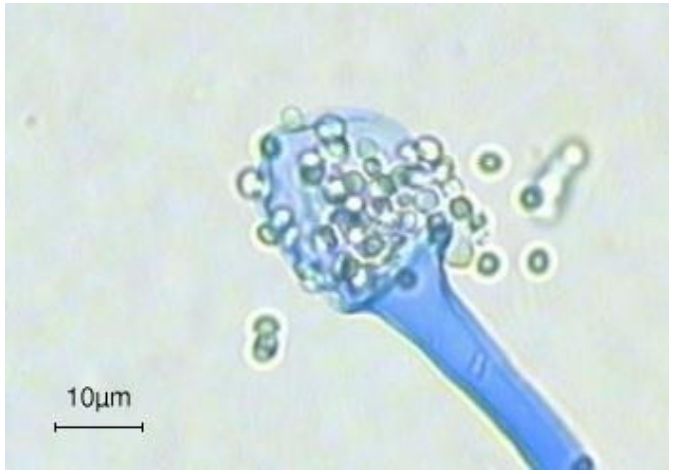
EUROPEAN HEMATOLOGY ASSOCIATION

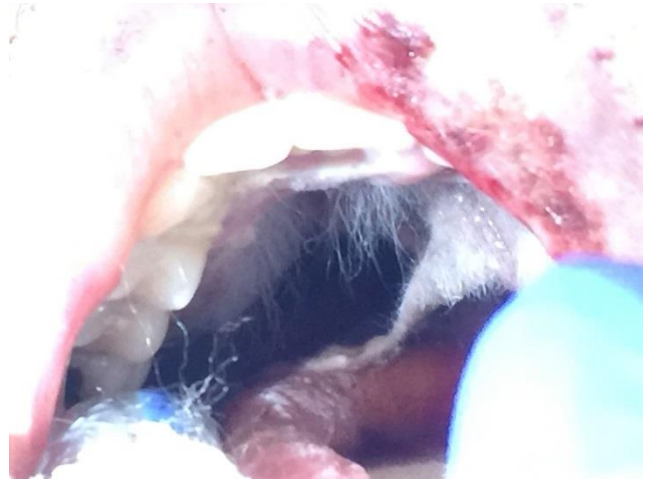
Ferrata Storti Foundation

Kombinasyon için öneri yok



Mukormikozis





ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2008, p. 2636–2638 Vol. 52, No. 7
0066-4804/08/$08.00+0 doi:10.1128/AAC.00492-08

Posaconazole Enhances the Activity of Amphotericin B against Hyphae of Zygomycetes In Vitro▽

Susanne Perkhofer,[1]* Maria Locher,[1] Manuel Cuenca-Estrella,[2] Reinhard Rüchel,[3] Reinhard Würzner,[1] Manfred P. Dierich,[1] and Cornelia Lass-Flörl[1]

Department of Hygiene, Microbiology and Social Medicine, Division of Hygiene and Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria[1]; Servicio de Micología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain[2]; and Department of Medical Microbiology and National Reference Center for Systemic Mycoses, University Hospital of Göttingen, Göttingen, Germany[3]

Received 15 April 2008/Returned for modification 20 April 2008/Accepted 25 April 2008

Medical Mycology September 2008, **46**, 567–573 informa healthcare

Comparative *in vitro* activities of posaconazole, voriconazole, itraconazole, and amphotericin B against *Aspergillus* and *Rhizopus*, and synergy testing for *Rhizopus*

SEVTAP ARIKAN*, BANU SANCAK*, SEHNAZ ALP*, GULSEN HASCELIK* & PAUL MCNICHOLAS†

**Hacettepe University Medical School, Department of Microbiology and Clinical Microbiology, Ankara, Turkey, and †Schering-Plough Research Institute, Kenilworth, New Jersey, USA*

- In vitro çalışmalarda posakonazol ve AmB arasında antagonizma olmadığı gösterilmiş
- Otuz klinik mukor izolatı kullanılarak yapılan çalışmada, kombinasyon conidia'lardan çok hiflere karşı daha sinerjistik (%10'a karşı %40, $p<0.05$)
- 11 *Rhizopus oryzae* izolatına karşı kombinasyon farklı değil, antagonizma yok

Hayvan Modelleri

- Farklı sonuçlar mevcut
- L-AmB + kaspofungin *Rhizopus oryzae* ile infekte diyabetik ketoasidozdaki farelerde survide iyileşme

Antimicrob Agents Chemother. 2005;49(2):830-2.

- L-AmB + anidulafungin veya mikafungin IV olarak *Rhizopus oryzae* ile infekte farelerde monoterapi ile karşılaştırıldığında survide iyileşme

Antimicrob Agents Chemother.2008;52(4):1556-8..

- L-AmB + posakonazol *Rhizopus oryzae* ile infekte farelerde kombine tedavi ile survide iyileşme yok

Antimicrob Agents Chemother. 2009;53(2):772-5.

Hayvan Modelleri

- AmB (0.3 mg/kg/g) + posakonazol (40 mg/kg/g) ile AmB 0.8 mg/kg/g – Survide uzama

Antimicrob Agents Chemother. 2008;52(10):3786-8..

- L-AmB, mikafungin ve deferasirox) fare mukormikozis –
  - Üçlü kombinasyon tüm diğer tedavilere göre (plasebo, tek ya da ikili tedavi) 28 gün survi açısından üstün (n=18/her grupta) (%40 survi-üçlü kombinasyonla vs. %0-11 diğer tedavilerle. p< 0.001

50th ICAAC, American Society for Microbiology, Boston, 2010 (Abstract M- 1094).

Published in final edited form as:
Clin Infect Dis. 2008 August 1; 47(3): 364–371. doi:10.1086/589857.

Combination Polyene-Caspofungin Treatment of Rhino-Orbital-Cerebral Mucormycosis

Caitlin Reed[1], Richard Bryant[2,3], Ashraf S. Ibrahim[1,3], John Edwards Jr.[1,3], Scott G. Filler[1,3], Robert Goldberg[2,3], and Brad Spellberg[1,3]
[1]Division of Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor–University

Logistic regression analyses for success at 30 days after hospital discharge.

Analysis, variable	Survival OR (95% CI)	P
Bivariate		
Combination therapy	9.0 (1.1–∞)	.03
ABLC vs. AmB or LAmB initial treatment	0.2 (0.06–0.9)	.03
CNS disease	0.3 (0.07–1.1)	.07
Maximum creatinine level	0.7 (0.5–1.0)	.05
Multivariate		
Combination therapy	10.9 (1.3–∞)	.02
ABLC vs. AmB or LAmB initial treatment	0.2 (0.02–1.6)	.17
CNS disease	0.3 (0.04–2.2)	.33
Maximum creatinine level	0.9 (0.5–1.4)	.66

Mukormikozis

Rehberler Ne Öneriyor?

ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of mucormycosis 2013

O. A. Cornely[1,†,‡,§], S. Arikan-Akdagli[2,‡,§], E. Dannaoui[3,§], A. H. Groll[4,†,‡,§], K. Lagrou[5,‡,§], A. Chakrabarti[6,§], F. Lanternier[7,8], L. Pagano[9], A. Skiada[10], M. Akova[2], M. C. Arendrup[11], T. Boekhout[12,13,14], A. Chowdhary[15], M. Cuenca-Estrella[16,†,‡], T. Freiberger[17,18,†], J. Guinea[19,†,‡], J. Guarro[20,‡], S. de Hoog[12,‡], W. Hope[21,†], E. Johnson[22,‡], S. Kathuria[15], M. Lackner[23,‡], C. Lass-Flörl[23,†,‡], O. Lortholary[7,†,‡], J. F. Meis[24,25,†,‡], J. Meletiadis[26,‡], P. Muñoz[19,†], M. Richardson[27,28,†,‡], E. Roilides[29,†,‡], A. M. Tortorano[30,‡], A. J. Ullmann[31,†,‡], A. van Diepeningen[12], P. Verweij[25,32,†,‡] and G. Petrikkos[33,†,‡,§]

TABLE 8. Recommendations on targeted first-line treatment of mucormycosis in adult patients

Population	Intention	Intervention	SoR	QoE	Comment
Any	To increase survival rates	Surgical debridement	A	IIu	*n* = 32
					n = 90
					n = 45
					n = 9
					n = 59
					n = 92, paediatric
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	IIu	*n* = 470
					n = 19
					n = 90
					n = 92, paediatric
Immunocompromised	To increase survival rates	Immediate treatment initiation	A	IIu	*n* = 70
Any	To cure and to increase survival rates	Amphotericin B, liposomal ≥5 mg/kg[a]	A	IIu	*n* = 4
					n = 16
					n = 5
					n = 21
					n = 28
					n = 130
					n = 40
					Animal model
					Animal model
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days[a]	A	II	Animal model
					Animal model
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg[a]	B	IIu	*n* = 10
					n = 7
					Animal model
					Animal model
Any	To cure	Posaconazole 4 × 200 mg/day or 2 × 400 mg/day[a]	B	IIu	*n* = 8
					n = 17
					Animal model
Any	To cure	Lipid-based amphotericin plus caspofungin[a]	C	III	*n* = 7
Any	To cure	Amphotericin B, deoxycholate, any dose[a]	D	I	Renal toxicity
					n = 9
					n = 532
					Renal toxicity
					n = 10
					n = 21

CNS, central nervous system; QoE, quality of evidence;

ESCMID AND ECMM PUBLICATIONS 10.1111/1469-0691.12371

ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of mucormycosis 2013

O. A. Cornely[1,†,‡,§], S. Arikan-Akdagli[2,‡,§], E. Dannaoui[3,§], A. H. Groll[4,†,‡,§], K. Lagrou[5,‡,§], A. Chakrabarti[6,§], F. Lanternier[7,8], L. Pagano[9], A. Skiada[10], M. Akova[2], M. C. Arendrup[11], T. Boekhout[12,13,14], A. Chowdhary[15], M. Cuenca-Estrella[16,†,‡], T. Freiberger[17,18,†], J. Guinea[19,†,‡], J. Guarro[20,‡], S. de Hoog[12,‡], W. Hope[21,†], E. Johnson[22,‡], S. Kathuria[15], M. Lackner[23,‡], C. Lass-Flörl[23,†,‡], O. Lortholary[7,†,‡], J. F. Meis[24,25,†,‡], J. Meletiadis[26,‡], P. Muñoz[19,†], M. Richardson[27,28,†,‡], E. Roilides[29,†,‡], A. M. Tortorano[30,‡], A. J. Ullmann[31,†,‡], A. van Diepeningen[12], P. Verweij[25,32,†,‡] and G. Petrikkos[33,†,‡,§]

TABLE 9. Recommendations on salvage treatment of mucormycosis in adult patients

Population	Intention	Intervention	SoR	QoE	Comment
Refractory to prior antifungal therapy	To cure	Posaconazole, oral suspension, 4 × 200 mg/day or 2 × 400 mg/day[a]	A	IIu	$n = 19$ $n = 81$[b] $n = 61$ $n = 15$[c]
Intolerant to prior antifungal	To cure	Posaconazole, oral suspension, 4 × 200 mg/day or 2 × 400 mg/day[a]	A	IIu	$n = 5$ $n = 43$[b] $n = 15$[c]
Intolerant to prior antifungal	To cure	Amphotericin B, liposomal, 5 mg/kg	B	IIu	$n = 8$
Refractory to prior antifungal therapy	To cure	Amphotericin B, lipid complex, 5 mg/kg	B	IIu	$n = 16$ $n = 23$
Intolerant to prior antifungal	To cure	Amphotericin B, lipid complex, 5 mg/kg	B	IIu	$n = 12$
Intolerant due to pre-existing renal disease	To cure	Amphotericin B, lipid complex, 5 mg/kg	B	IIu	$n = 18$
Intolerant due to pre-existing renal disease	To cure	Amphotericin B colloidal dispersion 5 mg/kg	B	IIu	$n = 21$
Refractory disease or intolerant to prior antifungal therapy	To cure	Polyene plus caspofungin	C	III	$n = 2$
Any	To cure	Polyene plus posaconazole	B	IIu	$n = 32$

GUIDELINE ARTICLE

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Samir Agrawal,[2] Livio Pagano,[3] Georgios Petrikkos,[4] Andreas H. Groll,[5] Anna Skiada,[6] Cornelia Lass-Flörl,[7] Thierry Calandra,[1] Claudio Viscoli[8] and Raoul Herbrecht[9]

EUROPEAN HEMATOLOGY ASSOCIATION
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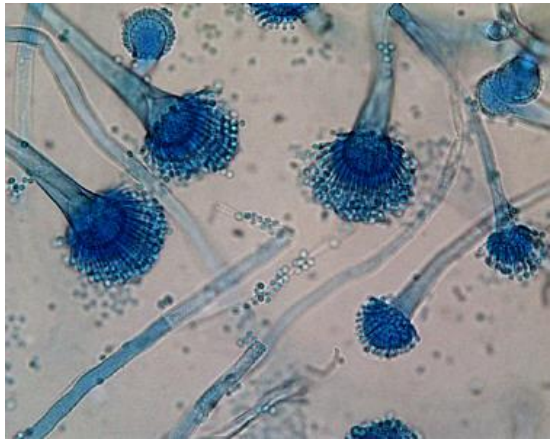
- Primer tedavi
  - Kombinasyon (CIII)
- Kurtarma tedavisi
  - LAmB + kaspofungin (BIII)
  - LAmB + posakonazol (BIII)



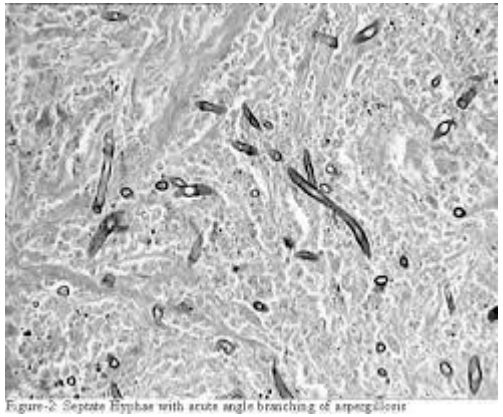
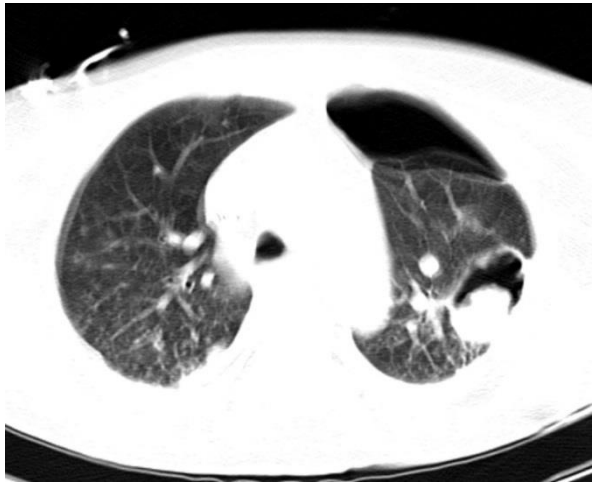
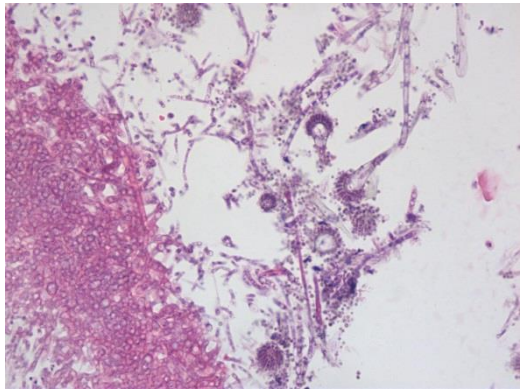


Figure-2 Septate Hyphae with acute angle branching of aspergillosis

Aspergilloz





Hayvan Modelleri

- Kaspofungin + vorikonazol dokudaki mikroorganizma miktarında 1000 kat azalma sağlıyor ve pozitif kültür sayısında istatistiksel olarak önemli derecede azalmaya neden oluyor

Kirkpatrick WR. Antimicrobial Agents and Chemother 2002;46:2564-8

- Kaspofungin + vorikonazol: Survide uzama, fungus yükü ve galaktomannan düzeyinde azalma

Zhang M Mycopathologia. 2014 Feb;177(1-2):11-8.

- Mikafungin + AmB, monoterapi ile karşılaştırıldığında survi oranı çok daha yüksek. Kombinasyon tedavisi ile akciğerdeki fungus yükünde ve serumda GM düzeylerinde azalma, önemli derecede histolojik iyileşme

Nagasaki Y. The Journal of Antimicrobial Chemotherapy 2009;64:379-82

Hayvan Modelleri

- Anidulafungin + vorikonazol kombinasyonu survide artış, pulmoner hasarda önemli derecede azalma, fungus yükünde azalma ile ilişkili

Petraitis V. The Journal of Infectious Diseases 2003;187:1834-43

- Anidulafungin + posakonazol – survide artış, böbrek yükünde azalma

Martin-Vicente A. Medical Mycology, 2017, 55, 457–460

- Anidulafungin + posakonazol - *A. fumigatus* – Fungus yükünde azalma, survide iyileşme

Bedin-Denardi L. Diagnostic Microbiology and Infectious Disease 90 (2018) 40–43

- Mikafungin + isavukonazol – fungus yükünde azalma, pulmoner hasarda azalma, survide uzama, galaktomannan ve (1→3)-β-d-glukan düzeylerinde azalma

Petraitis V. Antimicrobial Agents and Chemotherapy 2017;61 https://doi.org/ 10.1128/AAC.00305-17.

International Journal of Infectious Diseases 16 (2012) e76–e81

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Review

The role of combination antifungal therapy in the treatment of invasive aspergillosis: a systematic review

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Table 1
Characteristics of included studies

Reference	Study population	Sample size	Female, *n* (%)	Age range or mean (years)	Study design	Indication for combination therapy	Treatment category		Follow-up duration (weeks)	Outcome of combination vs. monotherapy	Adjusted effect estimates
							Combination	Monotherapy			
Popp et al., 1999[41]	Hematologic malignancy	21	8 (38)	44.95	Cohort	Primary	AMB 1 mg/kg/day + itraconazole 400 mg/day caps or suspension	AMB 1 mg/kg/day	NR	Favorable response	No adjusted analysis; univariate analysis: 82% vs. 50%, $p = 0.12$
Marr et al., 2004[20]	Hematologic malignancy	47	29 (61.7)	16–66	Cohort	Salvage	Voriconazole 6 mg/kg q12h IV for 1 day, then 4 mg/kg q12h ± caspofungin 70 mg IV for 1 day, then 50 mg/day	AMB 1 mg/kg/day and LFABs 5 mg/kg/day for those with pre-existing renal disease or intolerance to AMB	12	Mortality	HR 0.28, 95% CI 0.1–0.92
Kontoyiannis et al., 2005[13]	Hematologic malignancy	179	112 (62.6)	30–66	Cohort	Primary	LipoAMB 5 mg/kg/day + itraconazole 200 mg IV/PO bid, then 200 mg qd	LipoAMB 5 mg/kg/day	12	Favorable response	No adjusted analysis; univariate analysis: 0% vs. 10%, p = not significant
Singh et al., 2006[23]	Organ transplant recipients	87	36 (41.4)	19–68	Cohort	Primary	Voriconazole 6 mg/kg q12h IV for 1 day, then 4 mg/kg q12h + caspofungin 70 mg IV on day 1, then 50 mg/day	LipoAMB 5.2 mg/kg/day	12	Mortality	HR 0.58, 95% CI 0.3–1.14, $p = 0.11$
Upton et al., 2007[9]	Bone marrow transplant recipients	405	165 (40.7)	42.2	Cohort	Primary	Voriconazole ± caspofungin	Voriconazole (before 1996: AMB 0.5 mg/kg/day; after 1996: LipoAMB 5 mg/kg/day)	12	Mortality	HR 2.3, 95% CI 0.6–9.4, $p = 0.23$
Raad et al., 2008[39]	Hematologic malignancy	143	24 (16.8)	43.7	Cohort	Primary	HD-LPD/AMB ≥7.5 mg/kg/day ± caspofungin 70 mg on day 1 and 50–100 mg/day	Posaconazole (salvage) 400 mg PO q12h as outpatient or 200 mg by NG tube q6h or 800 mg q24h	12	Favorable response	OR 0.25, 95% CI 0.07–0.91, $p = 0.03$
Caillot et al., 2007[40]	Hematologic malignancy	30	9 (30)	16–75	RCT	Primary	LipoAMB 3 mg/kg/day IV + caspofungin 70 mg IV for 1 day, then 50 mg/day	LipoAMB 10 mg/kg/day	12	Favorable response	4/15 (27%) vs. 10/15 (67%), $p = 0.028$
Milhu et al., 2010[35]	Hematologic malignancy	141	54 (38.3)	9–79	Cohort	Salvage	L-AMB + echinocandin (90% caspofungin) (no dosage)	L-AMB (no dosage) or echinocandin (89% caspofungin) (no dosage)	12	Mortality	No adjusted estimates; 62% combination vs. 61% echinocandins vs. 67% L-AMB, $p = 0.78$
			39 (44)	9–80						Favorable response	No adjusted estimates; 21% combination vs. 28% echinocandins vs. 9% L-AMB, $p = 0.04$

AMB, conventional amphotericin B; bid, twice daily; 95% CI, 95% confidence interval; HD-LPD/AMB, high-dose lipid formulation of amphotericin B; HR, hazard ratio; IV, intravenous; L-AMB, lipid formulation of amphotericin B; LFABs, amphotericin B lipid complex or liposomal amphotericin B; LipoAMB, liposomal amphotericin B; NR, not reported; OR, odds ratio; NG tube, nasogastric tube; PO, per os (oral); q6 h, every 6 h; q12 h, every 12 h; q24 h, every 24 h; qd, four times daily; RCT, randomized controlled trial.

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Int J Infect Dis. 2014 November ; 28: 80–94. doi:10.1016/j.ijid.2014.07.007.

Salvage combination antifungal therapy for acute invasive aspergillosis may improve outcomes: a systematic review and meta-analysis

Anil A. Panackal[a,b,*], **Emilio Parisini**[c], and **Michael Proschan**[d]

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- Gözlemsel çalışma 14
  - Primer IA 9
  - Kurtarma 4
  - Her ikisi 1
- Tamamlanmış klinik çalışma 2
  - Primer 2
  - Kurtarma 0

Primer sonlanım noktası: 12 hafta survi

Published in final edited form as:
Int J Infect Dis. 2014 November ; 28: 80–94. doi:10.1016/j.ijid.2014.07.007.

Salvage combination antifungal therapy for acute invasive aspergillosis may improve outcomes: a systematic review and meta-analysis

Anil A. Panackal[a,b,*], **Emilio Parisini**[c], and **Michael Proschan**[d]

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- Primer tedavide kombinasyon üstün değil
- Kurtarma tedavisinde kombinasyon üstün
  - OR 1.90, %95 GA 1.04–3.46

Liposomal Amphotericin B in Combination With Caspofungin for Invasive Aspergillosis in Patients With Hematologic Malignancies

A Randomized Pilot Study (Combistrat Trial)

- Olası ya da kanıtlanmış IA
- Randomize, açık, pilot çalışma
- 15 olgu-Lipozomal AmB 10 mg/kg vs
- 15 olgu-Lipozomal AmB 3 mg/kg + kaspofungin

Liposomal Amphotericin B in Combination With Caspofungin for Invasive Aspergillosis in Patients With Hematologic Malignancies

A Randomized Pilot Study (Combistrat Trial)

Efficacy of Antifungal Treatment (Modified Intend-to-treat Population)

Parameter	No. of patients (%)	
	High-dose monotherapy group (n=15)	Combination group (n=15)
Overall treatment response at EOT		
Favorable	4 (27)	10 (67)*
Complete response	0	0
Partial response	4	10
Unfavorable	11 (73)	5 (33)
Stable response	6	4
Failure	4	1
Missing value	1	0
Time to favorable treatment response, d	4	10
Mean ± SD	14 ± 0.8	19.3 ± 9.3
Median [range]	14 [13–15]	14 [10–38]
Survival at EOT	14 (93)	15 (100)
Survival at Wk 12	12 (80)†	15 (100)

EOT indicates end of treatment; SD, standard deviation.

* $P = .028$ (favorable response high-dose monotherapy group vs combination group; chi-square test).

† Three deaths were caused by progression of the underlying hematologic condition (for 1 of those patients, fungal infection contributed to the death according to the investigator).

Vorikonazol vs Vorikonazol+Anidulafungin

- Randomize, çift kör, plasebo kontrollü
- Çok merkezli
- 93 merkez, 454 olgu
- Primer sonlanım – 6. hafta mortalite
- Sekonder sonlanım – 12. hafta mortalite

Ann Intern Med. 2015 Jan 20;162(2):81-9. doi: 10.7326/M13-2508.

- Mortalite oranı (6. hafta)
  - %19.3 (135 olgunun 26'sı) kombinasyon grubunda
  - %27.5 (142 olgunun 39'u) monoterapi
  - %95 GA, -19.0 to 1.5]; p = 0.087)
- Galaktomannan pozitifliği olan alt grupta mortalite (6 hafta)
  - %15.7 (108 olgunun 17'si) kombinasyon grubunda
  - %27.3 (110 olgunun 30'u) monoterapi grubunda
  - %95 GA -22.7 to -0.4, p = 0.037)

Ann Intern Med. 2015 Jan 20;162(2):81-9. doi: 10.7326/M13-2508.

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

A rescue therapy with a combination of caspofungin and liposomal amphotericin B or voriconazole in children with haematological malignancy and refractory invasive fungal infections

Deniz Yilmaz,[1] Can Balkan,[1] Yilmaz Ay,[1] Mehmet Akin,[1] Bulent Karapinar[2] and Kaan Kavakli[1]

[1]Pediatric Hematology Department, Ege University School of Medicine, Izmir, Turkey and [2]Ege University School of Medicine, Pediatric Intensive Care Unit, Izmir, Turkey

- 17 çocuk, 19
- Ortalama 12
  - 11 olguda
    - 4 hasta refrakter – kaspofungin + vorikonazol
  - 6 olguda LAmB stop – kaspofungin + vorikonazol

Başarı %68.4
12 hafta survi %75

Mycoses 2009; 54:234–42

International Journal of Antimicrobial Agents 45 (2015) 283–288

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Clinical experience of the use of voriconazole, caspofungin or the combination in primary and salvage therapy of invasive aspergillosis in haematological malignancies

Issam I. Raad*, Aline El Zakhem, Gilbe
Ray Hachem

*Department of Infectious Diseases, Infection Control and Employe
Houston, TX 77030, USA*

- 181 IA –
- 134'ü ar
  - Prime
    - 1
    - 3
    - 33 kaspofungin + vorikonazol
  - Kurtarma tedavisi
    - 17 kaspofungin
    - 24 vorikonazol
    - 35 kaspofungin + vorikonazol

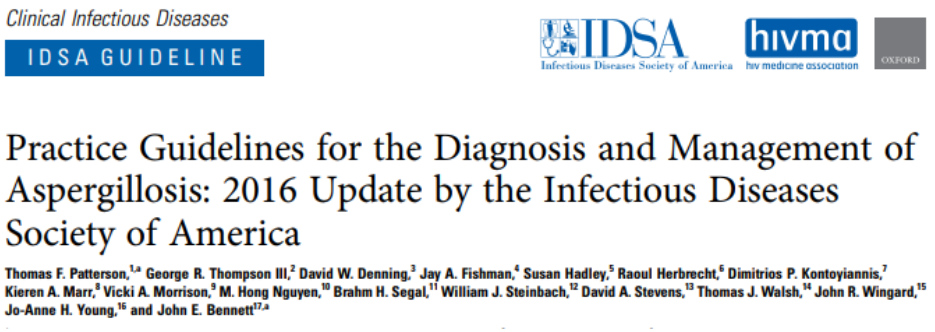
Daha ileri düzeyde, prospektif, randomize çalışmalara ihtiyaç var
Önceki iki çalışma ışığında kombinasyon etkili olabilir

unda mortalite daha
terval 0.06–0.96; P = 0.04

Kombinasyon tedavisinde vorikonazole üstünlük yok, tekli tedavide vorikonazol grubunda mortalite kaspofungin grubundan düşük

Aspergilloz

Rehberler Ne Öneriyor?



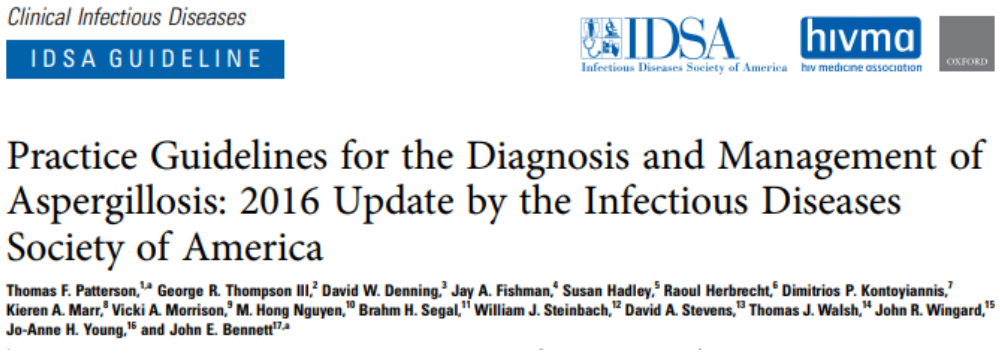
- Mevcut tedaviye ekleme tedavi seçeneği yokluğunda anlaşılabilir bir durumdur
- İlaç kombinasyonları ile ilgili çalışma sayısı sınırlı ve daha fazla veriye ihtiyaç var

Clinical Infectious Diseases
IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

- Kombinasyon – Preklinik ve Laboratuvar Çalışmalar
  - Polyenler + azol ya da ekinokandinler bazı preklinik çalışmalarda additif ya da sinerjistik etkili
  - Ancak test yöntemleri farklı ve sonuçlar çelişkili – bulguları yorumlamak zor (zayıf öneri; düşük kanıt düzeyi)



- Refrakter ya da Progresif Aspergilloz – Kurtarma Tedavisi
  - Mevcut tedaviye bir antifungal ajan eklenebilir ya da başlangıç rejimi dışındaki sınıflardan antifungal ajan kombinasyonu yapılabilir (zayıf öneri, orta kanıt düzeyi)
  - Kurtarma tedavisinde kullanılabilecek ajanlar: LAmB, mikafungin, kaspofungin, posakonazol veya itrakonazoldür (güçlü öneri; orta kanıt düzeyi)
  - Başlangıçtaki triazol tedavisine yanıtsızlık varsa LAmB ± ekinokandin düşünülmelidir

GUIDELINE ARTICLE

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Samir Agrawal,[2] Livio Pagano,[3] Georgios Petrikkos,[4] Andreas H. Groll,[5] Anna Skiada,[6] Cornelia Lass-Flörl,[7] Thierry Calandra,[1] Claudio Viscoli[8] and Raoul Herbrecht[9]

EUROPEAN HEMATOLOGY ASSOCIATION
Ferrata Storti Foundation

- Primer tedavi
  - Vorikonazol + anidulafungin (CI)
  - Diğer kombinasyonlar (CIII)
- Kurtarma tedavisi
  - Kombinasyon (BII)

ARTICLE IN PRESS

Clinical Microbiology and Infection xxx (2018) e1–e38

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Table 27
Targeted therapy of pulmonary disease—first line

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment
1] Neutropenia (non-allo HSCT recipients) 2] Allo-HSCT (during neutropenia) 3] Allo-HSCT (w/o neutrop other nc neutrop patients	To increase response and survival rate	Isavuconazole 200 mg IV tid day 1–2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis fewer adverse effects than voriconazole
		Voriconazole 2× 6 mg/kg IV (oral 400 mg bid) on day 1, then 2–4 mg/kg	A	I	II_t	II_t	C III for start with oral; D III, if prior mould active azole
		by 50 mg qd (if body weight <80 kg)					
		Itraconazole 200 mg q12 h IV on day 1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III	
		Micafungin 100 mg	C	III	III	III	
		AmB colloidal dispersion (ABCD) 4–6 mg/kg	D	I	II_t	II_t	
		Conventional AmB 1–1.5 mg/kg	D	I	II_t	II_t	
		Other combinations	D	III	III	III	Efficacy unproven
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III	

Vorikonazol + Anidulafungin (CI)
Diğer kombinasyonlar (DIII)

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Original ar

Diagnos
summa

A. fumigatus vorikonazol MIC =2 mg/L (IM) ile infekte hastaların vorikonazol monoterapisine daha az yanıt verip vermedikleri net değil. Bu hastalarda tedavi yetersizliği olasılığı yüksek olduğundan invaziv aspergilloz durumunda ekinokandin ya da LAmB ile kombine tedavi düşünülmeli (AIII)

Table 20
Optimal therapy in documented azol

Population			Ref.
Isolate with voriconazole MIC = 2 mg/mL		combination therapy or L-AmB monotherapy for IA (as well as for CPA)	treatment failure may be higher than in voriconazole MIC <2	[529–532]
Isolate with voriconazole MIC >2 mg/mL				[113,114,533] No reference found. [529] [534] No reference found.

Çevre izolatlarında azol direnci <%10 ise yaklaşım primer tedavi şeklinde. Azol direnci >%10 ise primer tedavide vorikonazol + ekinokandin (BIII) veya vorikonazol + LAmB (BIII)

Abbreviations: AmB, Amphotericin B Quality of evidence; SoR, Strength of recommendation.

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Original article

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Table 32
Treatment in non-haematological patients

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
HIV	To treat IA	Voriconazole	A	III	Consider drug–drug interactions with antiretroviral drugs.	[620]
SOT Heart						[621]
SOT, any						[170,214,287,333, 600,622–624,625–627]
					monitor liver function tests especially in liver transplant recipients.	
OT, any	To treat IA	L-AmB	A	II		[628–630]
SOT, any	To treat IA	Voriconazole & caspofungin	B	II	40 SOT voriconazole & caspofungin ($n = 40$) vs amphotericin B ($n = 47$). Survival benefit in patients with *A. fumigatus* or renal insufficiency	[289]
SOT, if voriconazole contraindicated	To treat IA	Caspofungin	B	III	Complete response 83%; response 7/9 monotherapy and 7/10 combination	[631–634]

SOT
Vorikonazol + Kaspofungin (BII)

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Original article

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Table 37
Antifungal drugs in refractory disease

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Haematological patients with refractory IA	Achieve complete or partial response or stabilization or improvement	Switch to another drug class	A	III		
		Any combination	C	III	No prospective study demonstrated	[715]
						[333,716,624,717]
						[676,718,719]
						[570,719,720,628]
		ABCD			No longer commercially available	[721,722]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	B	II	Very few data in case of voriconazole/ posaconazole failure	[335,717,723–727,633,728]
		Micafungin 75–200 mg qd	C	II		[572,729]
		Posaconazole 200 mg qid or 400 mg bid suspension or 300 mg tablet bid day 1, followed by 300 mg qd	B	II		[138,336,730,731]
		Itraconazole	D	III	In case of refractoriness to voriconazole	
		Itraconazole oral forms	C	II	Poor bioavailability	[126]
		Itraconazole IV formulation			Commercially not available everywhere	[537,732]

Tedaviye dirençli – Herhangi bir kombinasyon (CIII)

Özet

- Kriptokok infeksiyonları
- Kandida infeksiyonları
  - Endokardit, menenjit, endoftalmit
- Mukormikozis
  - Primer tedavide kanıt düzeyi düşük
  - Kurtarma tedavisinde öneri
- Aspergilloz
  - Primer tedavide kanıt düzeyi düşük
  - Kurtarma tedavisinde etkili olabilir
  - Azol IM ya da dirençli izolatlarda kullanılabilir