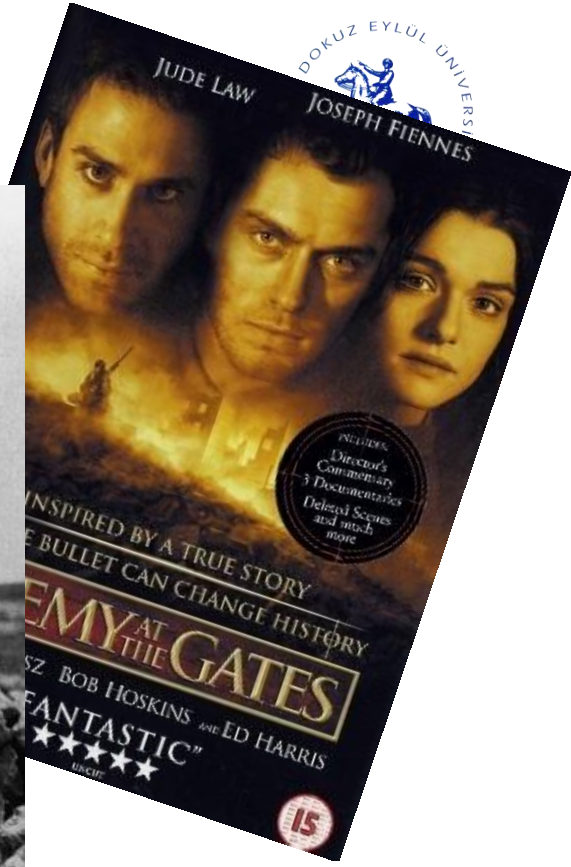
İnvazif Kandida İnfeksiyonları Tedavi

Prof. Dr. Nur YAPAR

DEÜTF İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji A.D.

28 MART 2015

Sunum Planı



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Düşman: Birinin kötülüğünü isteyen, ondan nefret eden, ona zarar vermeye çalışan kimse, yağı, hasım, antagonist, **dost** karşıtı

IFI Etkenleri

Candida spp.	*C. albicans*
	C. glabrata
	C. gulliermondii
	C. kefyr
	C. krusei
	C. lusitaniae
	C. rugosa
	C. parapsilosis
	C. tropicalis
Aspergillus spp.	*A. fumigtus*
	A. niger
	A. flavus
	A. terreus
Other hyaline moulds	*Acremonium* spp.
	Fusarium spp.
	Paecilomyces spp.
	Scedosporium spp.
	Scopulariopsis spp.
	Trichoderma spp.
Other yeasts	*Blastoschizomyces* spp.
	Cryptococcus neoformans
	Malassezia spp.
	Rhodotorula spp.
	Saccharomyces spp.
	Trichosporon spp.
Zygomycetes	*Absidia* spp.
	Cunninghamella spp.
	Mucor spp.
	Rhizomucor spp.
	Rhizopus spp.
Dematiaceous moulds	*Alternaria* spp.
	Bipolaris spp.
	Curvularia spp.
	Cladophialophora spp.
	Exophiala spp.
	Phialophora spp.

Richardson M, et al. *CMI* 2008

Candida spp

- >150 tür
- Yaklaşık 17 tür insanda infeksiyon etkeni
  - En sık *C. albicans*
  - İnvazif infeksiyonların % 90'ı;
    - *C. albicans*
    - *C. glabrata*
    - *C. parapsilosis*
    - *C. tropicalis*
    - *C. krusei*

Toplam Hİ Oranı (%)	Hİ Sayısı	KDİ	*Candida* KDİ	*Candida* KDİ Ölüm
2.5	875.000	87.500	7000	2800
5	1.750.000	175.000	14.000	5600
10	3.500.000	350.000	28.000	11.200

Atfedilen mortalite %40, yatış süresi ortalama 22 gün uzun
Maliyet; 40.000 $

Wenzel RP,et al. *Clin Infect Dis* 2005

MAJOR ARTICLE

The Epidemiology and Attributable Outcomes of Candidemia in Adults and Children Hospitalized in the United States: A Propensity Analysis

Theoklis E. Zaoutis,[1,2,5] Jesse Argon,[1] Jaclyn Chu,[1,2] Jesse A. Berlin,[4,a] Thomas J. Walsh,[6] and Chris Feudtner[1,3]

Table 3. Outcomes attributable to candidemia in the United States, 2000.

	Pediatric patients			Adult patients		
Variable	With candidemia (n = 1118)	Without candidemia (n = 2062)	Attributable increase (95% CI)	With candidemia (n = 8949)	Without candidemia (n = 17,267)	Attributable increase (95% CI)
Mortality, %	15.8	5.9	10.0 (6.2–13.8)	30.6	16.1	14.5 (12.1–16.9)
Length of stay, mean no. of days per patient	44.8	23.7	21.1 (14.4–27.8)	18.6	8.5	10.1 (8.9–11.3)
Total charges, mean US$ per patient	183,645	91,379	92,266 (65,058–119,474)	66,154	26,823	39,331 (33,60–45,602)

Klinik Tablolar

- Kandidemi
- Akut dissemine kandidiyaz
- Kronik dissemine kandidiyaz (Hepatosplenik)
- Diğer
  - Endokardit
  - Osteomyelit
  - Septik artrit
  - Tenosinovit
  - Endoftalmit
  - Menenjit

Planlama

1. İzlem. 2. Bir ulusun veya uluslar topluluğunun, barış ve savaşta benimsenen politikalara destek vermek amacıyla politik, ekonomik, psikolojik ve askerî güçleri bir arada kullanma bilimi ve sanatı, sevkülceyş.

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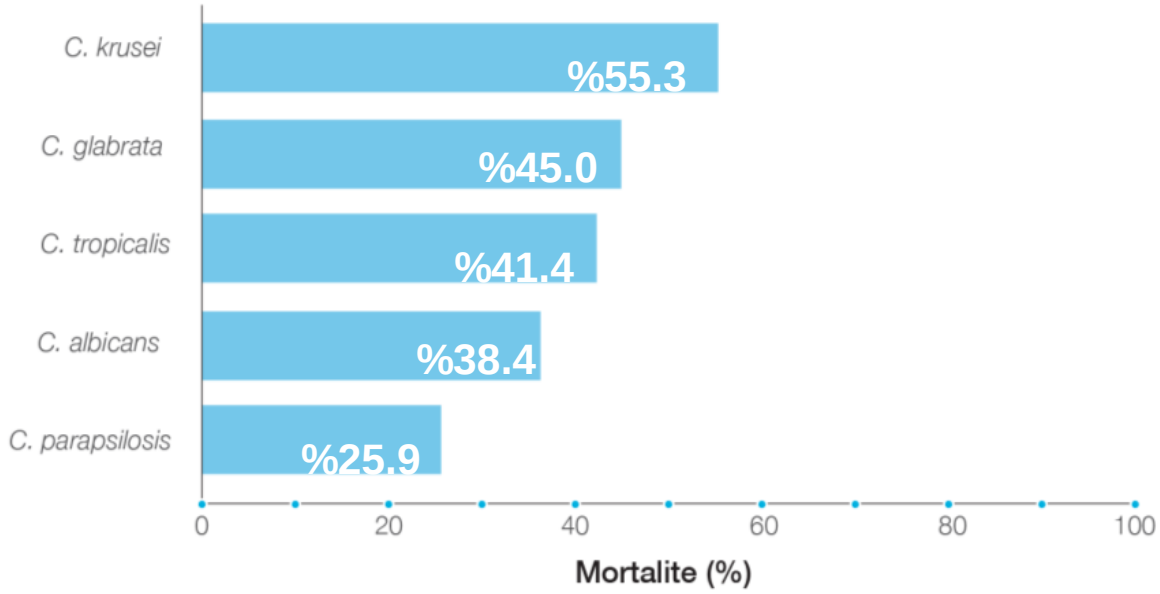
Bilinmesi Gerekenler

- Lokal epidemiyolojik veriler
  - Türlerin dağılımı ve duyarlılığı
- Azol kullanımı öyküsü
- Mevcut kliniğin ciddiyeti
  - Sepsis, ağır sepsis, septik şok veya organ tutulumu
- Nötropeni
- Organ yetmezliği
- Antifungallere karşı aşırı duyarlılık veya intolerans
- Kullanılan diğer ilaçlar (toksisite, etkileşim)

Kandidemide Etkenle İlişkili Mortalite

Kandidemilerin 30. gündeki mortalitesi



Tortorano A, et al. Eur J Clin Microbiol Infect Dis. 2004;23(4):317-22

İnvazif Kandidiyazda Etken Dağılımı (ARTEMIS 2003)

***C. albicans* ↓**

***C. tropicalis* ↑**
***C. parapsilosis* ↑**
***C. krusei* ↑**

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TABLE 7. Species distribution of *Candida* from cases of inva

Species	% of total no. of case					
	1997–1998	1999	2000	2001	2002	2003
C. albicans	73.3	69.8	68.1	65.4	61.4	62.3
C. glabrata	11.0	9.7	9.5	11.1	10.7	12.0
C. tropicalis	4.6	5.3	7.2	7.5	7.4	7.5
C. parapsilosis	4.2	4.9	5.6	6.9	6.6	7.3
C. krusei	1.7	2.2	3.2	2.5	2.6	2.7
C. guilliermondii	0.5	0.8	0.8	0.7	1.0	0.8
C. lusitaniae	0.5	0.5	0.5	0.6	0.5	0.6
C. kefyr	0.2	0.4	0.5	0.4	0.4	0.5
C. rugosa	0.03	0.03	0.2	0.7	0.6	0.4
C. famata	0.08	0.2	0.5	0.2	0.4	0.3
C. inconspicua			0.08	0.1	0.2	0.3
C. norvegensis			0.08	0.1	0.07	0.1
C. dubliniensis			0.01	0.08	0.1	0.05
C. lipolyti			0.06	0.06	0.06	0.08
C. zeylano			0.03	0.08	0.02	0.04
C. pellicul				0.06	0.05	0.04
Candida s		6.0	3.7	3.3	7.9	4.9
Total no. of cases	22,533	20,998	11,698	21,804	24,680	33,002

***C. glabrata* ↔**

Pfaller MA, et al. Clin Microbiol Rev 2007

- DEÜ Anestezi ve Reanimasyon Yoğun Bakım Ünitesi 2004-2008
  - *C. albicans* % 53
  - *C. parapsilosis* % 21.2
  - *C. tropicalis* % 7.6
  - *C. glabrata* % 6.1
  - *C. utilis* % 6.1
  - *C. lusitaniae* % 3.0
  - *C. krusei* % 1.5
  - *C. kefyr* % 1.5

Yapar N, et al. Anaesth, Pain and Intensive Care, 2014

Türkiye Verileri

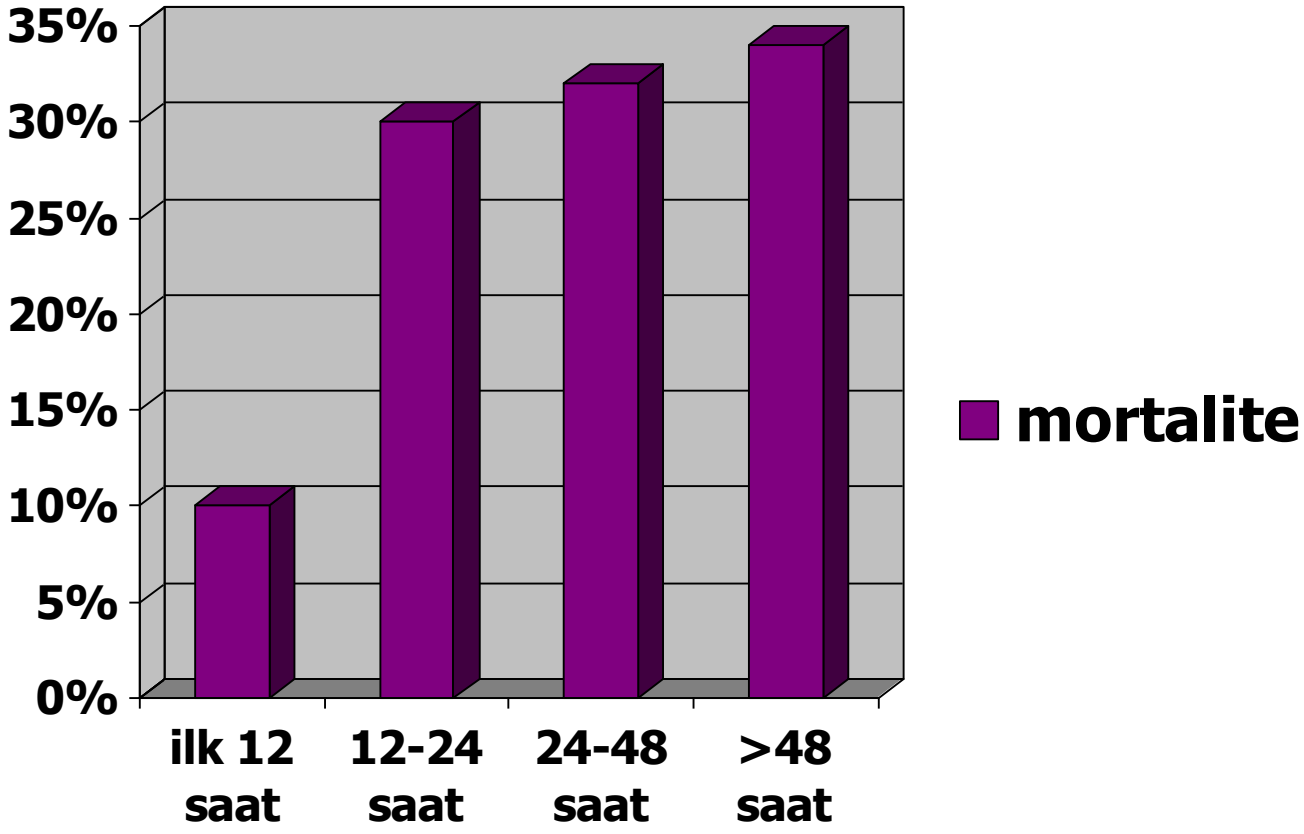
- 2008 yılı bölgemizde
  - *C. albicans* % 45.8
  - *C. tropicalis* % 24.1.
  - *C. parapsilosis* % 14.5
  - *C. glabrata* % 4.8
  - *C. kefyr* % 3.6
  - *C. krusei* % 2.4
  - Diğer % 4.8

Yapar N et al. Med Mycol 2011

Relation Initiation Antifungal Therapy and Outcome of Candidemia

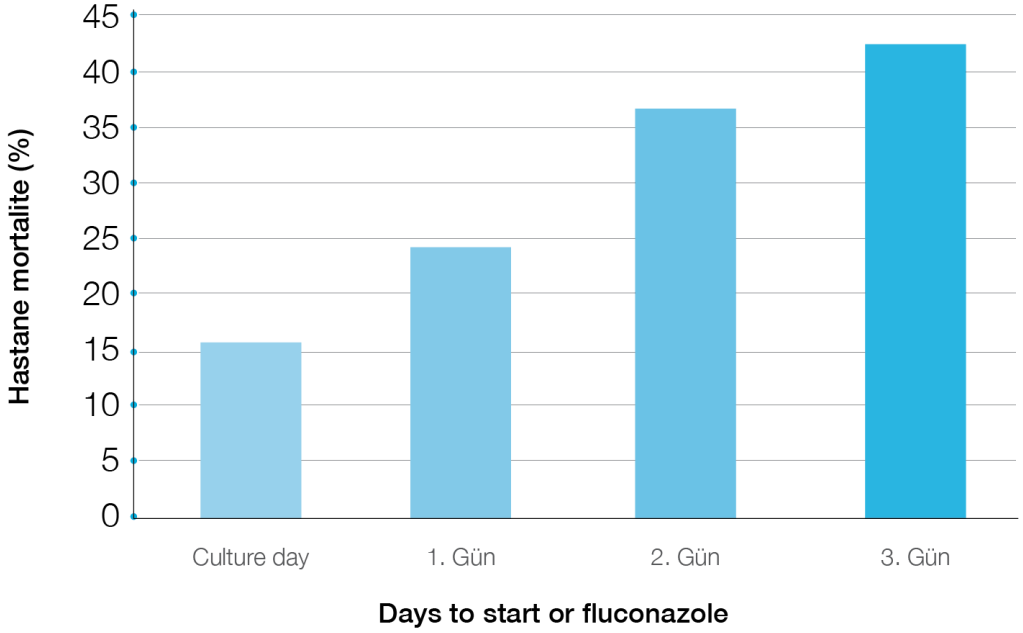
Morrell et al. AAC 2005; 49:3640-3645

134 kandidemi olgusu



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

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



Garey KW, Clin Infect Dis 2006;43:25

DOKUZ EYLÜL ÜNİVERSİTESİ
İZMİR-1982

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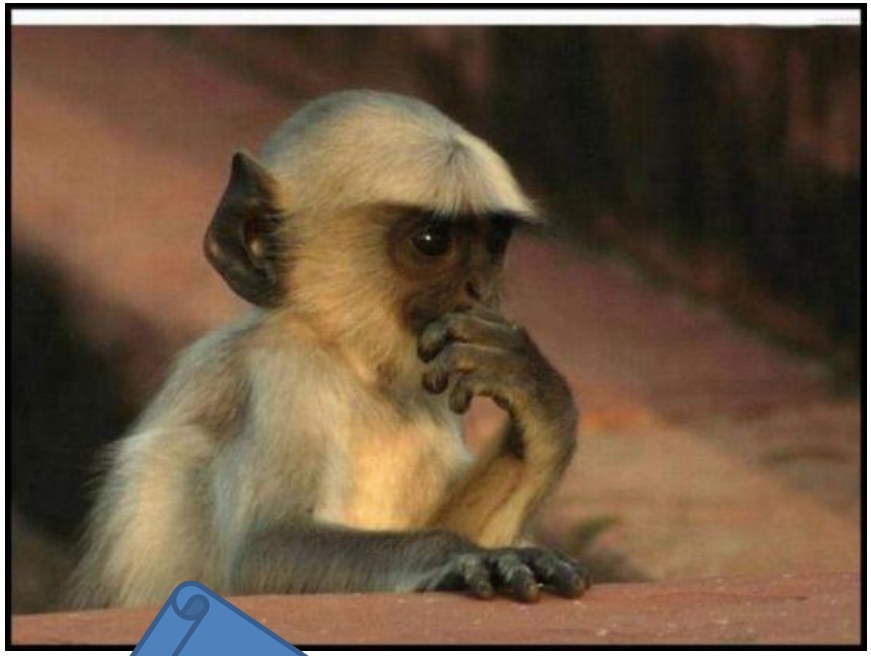

NAPCAZ ŞİMDİ?

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DOKUZ EYLÜL ÜNIVE

IDSA GUIDELINES

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

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

[1]University of Alabama at Birmingham, Birmingham; [2]University of Michigan and Ann Arbor Veterans Administration Health Care System, Ann Arbor, and [3]Wayne State University, Detroit, Michigan; [4]University of Wisconsin, Madison; [5]Duke University Medical Center, Durham, North Carolina; [6]Harbor–University of California at Los Angeles Medical Center, Torrance; [7]Medical College of Georgia, Augusta; [8]University of Texas at Houston, Houston; [9]Cooper Hospital, Camden, New Jersey; [10]National Cancer Institute, Bethesda, Maryland; [11]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [12]Nijmegen University Centre for Infectious Diseases, Nijmegen, The Netherlands; and [13]Astra Zeneca Pharmaceuticals, Manchester, United Kingdom

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Nötropenik Olmayan Hastada Kandidemi

Non-Culture-Based Diagnostic Techniques

Several new diagnostic techniques offer promise for the early diagnosis of invasive candidiasis. Several of these assays are approved as adjuncts to the diagnosis of invasive candidiasis, but their role in clinical practice is poorly defined. Several other assays are under development but are not yet approved (see below).

RECOMMENDATIONS FOR THE MANAGEMENT OF CANDIDIASES

I. WHAT IS THE TREATMENT OF CANDIDEMIA IN NONNEUTROPENIC PATIENTS?

Recommendations

1. Fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) is recommended as initial therapy for most adult patients (A-I). The Expert Panel favors an echinocandin for patients with moderately severe to severe illness or patients who have had recent azole exposure (A-III). Fluconazole is recommended for patients who are less critically ill and who have no recent azole exposure (A-III). The same therapeutic approach is advised for children, with attention to differences in dosing regimens (B-III).
2. Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are clinically stable (A-II).
3. For infection due to *C. glabrata*, an echinocandin is preferred (B-III). Transition to fluconazole or voriconazole is not recommended without confirmation of isolate susceptibility (B-III). For patients who initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing an azole to completion of therapy is reasonable (B-III).
4. For infection due to *C. parapsilosis*, fluconazole is recommended (B-III). For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable (B-III).
5. AmB-d (0.5–1.0 mg/kg daily) or LFAmB (3–5 mg/kg daily) are alternatives if there is intolerance to or limited availability of other antifungal agents (A-I). Transition from AmB-d or LFAmB to fluconazole therapy is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are clinically stable (A-I).
6. Voriconazole (400 mg [6 mg/kg] twice daily for 2 doses, then 200 mg [3 mg/kg] twice daily) is effective for candidemia (A-I), but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata* (B-III).
7. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia (A-III).
8. Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia (A-II).

Evidence Summary

The selection of any particular agent for the treatment of candidemia should optimally take into account any history of recent azole exposure, a history of intolerance to an antifungal agent, the dominant *Candida* species and current susceptibility data in a particular clinical unit or location, severity of illness, relevant comorbidities, and evidence of involvement of the CNS, cardiac valves, and/or visceral organs. Early initiation of effective antifungal therapy is critical in the successful treatment of candidemia, as demonstrated by recent data suggesting higher mortality rates among patients with candidemia whose therapy was delayed [77, 78].

Fluconazole remains standard therapy for selected patients with candidemia, on the basis of abundant data from well-designed clinical trials [27, 28, 53, 79]. There is little role for itraconazole in this setting, given similar antifungal spectrum, ease of administration, superior pharmacokinetics, and better tolerability of fluconazole. Fluconazole should be considered first-line therapy for patients who have mild to moderate illness (i.e., are hemodynamically stable), who have no previous exposure to azoles, and who do not belong in a group at high risk of *C. glabrata* (infection e.g., elderly patients, patients with cancer, and patients with diabetes). Patients with candidemia and suspected concomitant endocardial or CNS involvement should probably not receive fluconazole as initial therapy; rather, they should receive an agent that is fungicidal, such as AmB (for endocardial or CNS candidiasis) or an echinocandin (for endocardial candidiasis). On the basis of data from recent clinical trials [28, 51, 52, 54, 79], step-down therapy to fluconazole is reasonable for patients who have improved clinically after initial therapy with an echinocandin or AmB and who are infected with an organism that is likely to be susceptible to fluconazole (e.g., *C. albicans*, *C. parapsilosis*, and *Candida tropicalis*).

The echinocandins demonstrate significant fungicidal activity against all *Candida* species, and each has demonstrated success in ~75% of patients in randomized clinical trials. Because of their efficacy, favorable safety profile, and very few drug interactions, the echinocandins are favored for initial therapy for patients who have a recent history of exposure to an azole,

1. Erişkin hastaların çoğu için flukonazol veya bir ekinokandin önerilir (AI)

Öncesinde azol kullanımı olan veya ağır kliniği olan hastalarda ekinokandin önerilir (AIII). Hafif klinik tablo veya azol kullanımı yoksa flukonazol önerilir

Aynı öneriler çocuk hastalar için de geçerlidir

Nötropenik Olmayan Hastada Kandidemi

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2.İzole edilen etken *C. albicans* gibi flukonazole duyarlı bir köken ve hastanın kliniği stabilse ekinokandinden flukonazole geçilebilir (A-II).

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3. *C. glabrata* için ekinokandin (B-III). Azol duyarlılığı öğrenilmeden flukonazol veya vorikonazole geçiş önerilmez (B-III). Ampirik olarak azol başlanmışsa klinik ve mikrobiyolojik yanıt varsa devam edilebilir (B-III).

Nötropenik Olmayan Hastada Kandidemi

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4. *C. parapsilosis* için flukonazol önerilir (B-III). Ampirik olarak ekinokandin başlanmışsa klinik ve mikrobiyolojik yanıt varsa devam edilebilir (B-III).

Nötropenik Olmayan Hastada Kandidemi

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5. Diğer ajanlara intolerans veya kısıtlı yararlanım söz konusu ise AmB-d veya LFAmB alternatif (A-I).İzole edilen etken *C. albicans* gibi flukonazole duyarlı bir köken ve hastanın kliniği stabilse Amfoterisin B'den flukonazole geçilebilir (A-I).

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6. Kandidemide vorikonazol etkilidir(A-I), ancak flukonazole üstünlüğü fazla değil ve *Candida krusei* veya *Candida glabrata* fungemisinde orale geçişte önerilir (B-III).

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8. Kateterin çıkarılması (A-II)

ESCMID PUBLICATIONS 10.1111/1469-0691.12039

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients

O. A. Cornely[1†], M. Bassetti[2†], T. Calandra[3†], J. Garbino[4†], B. J. Kullberg[5†], O. Lortholary[6,7†], W. Meersseman[8†], M. Akova[9], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[5], A. H. Groll[4], R. Herbrecht[15], W. W. Hope[16], H. E. Jensen[17], C. Lass-Flörl[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[5], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

28 MART 2015

- Ampirik tedavi
- Etkene yönelik tedavi
- Yoğun bakım hastasına dikkat
- Öneri düzeylerinde faklılık

Ampirik-Preemptif Tedavi

TABLE 4. Recommendations on fever-driven and diagnosis-driven therapy of candidaemia and invasive candidiasis

Population	Intention	Intervention	SoR	QoE
Adult ICU patients with fever despite broad-spectrum antibiotics and APACHE II >16	To resolve fever	Fluconazole 800 mg/day	D	I
ICU patients persistently febrile, but without microbiological evidence	To reduce overall mortality	Fluconazole or echinocandin	C	II_u
ICU patients with candida isolated from respiratory secretions	To cure invasive candidiasis or candidaemia early	Any antifungal	D	II_u
ICU patients with positive (1,3)-β-D-glucan test[a]	To cure invasive candidiasis or candidaemia early	Any antifungal	C	II_u
Any patient with *Candida* isolated from a blood culture	To cure invasive candidiasis	Antifungal treatment	A	II

Etkene Yönelik

TABLE 5. Recommendations on initial targeted treatment of candidaemia and invasive candidiasis in adult patients

Intervention	SoR	QoE	References	Comment
	A	I	[64]	Consider local epidemiology (*Candida parapsilosis*, *Candida krusei*), less drug–drug interactions than caspofungin
	A	I	[67] [55] [63]	Consider local epidemiology (*C. parapsilosis*)
	A	I	[61] [63]	Consider local epidemiology (*C. parapsilosis*), less drug–drug interactions than caspofungin, consider EMA warning label
	B	I	[61] [62]	Similar efficacy as micafungin, higher renal toxicity than micafungin
	B	I	[43] [78] [77]	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg[a]	C	I	[165] [53] [74] [54] [64] [76] [75] [73] [72]	Limited spectrum, inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against *C. parapsilosis*
Amphotericin B lipid complex 5 mg/kg	C	II_a	[57] [58]	
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	[50] [51] [165] [53] [54] [55]	Substantial renal and infusion-related toxicity
Amphotericin B deoxycholate plus fluconazole	D	I	[74]	Efficacious, but increased risk of toxicity in ICU patients No survival benefit
Amphotericin B deoxycholate plus 5-fluorocytosine	D	II	[75]	
Efungumab plus lipid-associated amphotericin B	D	II	[166]	
Amphotericin B colloidal dispersion	D	II_a	[60]	
Itraconazole	D	II_a	[76]	
Posaconazole	D	III	No reference found	

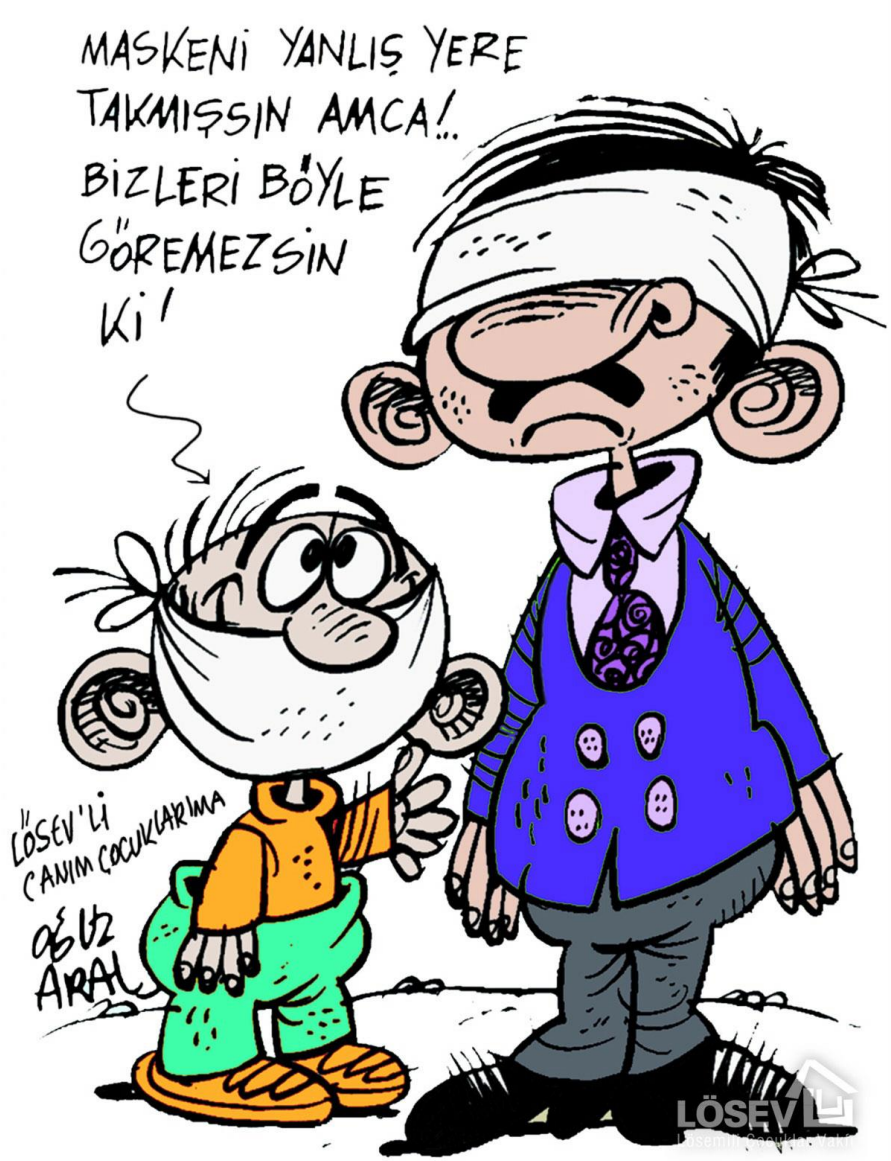
Ekinokandinler

LAmB
Vorikonazol

Kateter Değişimi

- Kandidemi durumunda değişmeli AII

- Ancak Ekinokandin, LFAmB kullanılıyorsa değişmeyebilir B II


MASKENİ YANLIŞ YERE TAKMIŞSIN AMCA!.. BİZLERİ BÖYLE GÖREMEZSİN Kİ!
LÖSEV'Lİ CANIM ÇOCUKLARIMA
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LÖSEV

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DOKUZ EYLÜL ÜNİVERSİTESİ
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IDSA GUIDELINES

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

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moderately severe to severe illness (i.e., are hemodynamically unstable), allergy or intolerance to azoles or AmB, or high risk of infection with *C. krusei* or *C. glabrata*. A short course of intravenous echinocandin therapy (3–5 days) followed by transition to oral fluconazole or voriconazole (for *C. krusei* infection) is a reasonable approach to the treatment of candidemia in the stable patient, but there are few clinical data to support this management strategy. The Expert Panel favors fluconazole over the 3 available echinocandins for treatment of candidemia due to *C. parapsilosis* on the basis of the decreased in vitro activity of echinocandins against *C. parapsilosis* [45, 46] and reports of echinocandin resistance among selected isolates [80]. Most experts agree that the echinocandins are sufficiently similar to be considered interchangeable.

Data from a recent randomized study suggest that an echinocandin may be superior to fluconazole as primary therapy for candidemia [53]. Although many experts agree that an echinocandin is favored as initial therapy for patients with moderately severe to severe disease due to invasive candidiasis, few agree that an echinocandin is favored for all episodes, and it is reasonable to consider the history of recent azole exposure, severity of illness, and the likelihood of fluconazole resistance in making a choice for initial antifungal therapy.

Voriconazole was shown to be as effective as AmB induction therapy for 4–7 days, followed by fluconazole for candidemia and invasive candidiasis [79]. Voriconazole possesses activity against most *Candida* species, including *C. krusei* [26, 81], but the need for more-frequent administration, less predictable pharmacokinetics, more drug interactions, and poor tolerance to the drug, compared with other systemic antifungals, make it a less attractive choice for initial therapy. Voriconazole does not provide predictable activity against fluconazole-resistant *C. glabrata* [26, 81]. It does, however, fill an important niche for patients who have fluconazole-resistant isolates of *C. krusei*, *C. guilliermondii*, or *C. glabrata* that have documented voriconazole susceptibility and who are ready for transition from an echinocandin or AmB to oral therapy.

Posaconazole has excellent in vitro activity against most *Candida* species, but there are few clinical data to support its use among patients with candidemia. On the basis of available data and the lack of an intravenous formulation, it is difficult to envision a significant role for posaconazole in the treatment of candidemia, other than in select patients for whom transition to an expanded-spectrum azole is warranted.

AmB-d is recommended as initial therapy when alternative therapy is unavailable or unaffordable, when there is a history of intolerance to echinocandins or azoles, when the infection is refractory to other therapy, when the organism is resistant to other agents, or when there is a suspicion of infection due to non-*Candida* yeast, such as *Cryptococcus neoformans*. L-AmB at doses of 3 mg/kg daily has been shown to be effective for treatment of candidemia, based on a recent prospective clinical trial [52]. Similarly, ABLC administered at 3 mg/kg/day has been successfully used for the treatment of candidemia (E. J. Anaissie, unpublished data). Infections due to *Candida lusitaniae* are uncommon; for this organism, the Expert Panel favors the use of fluconazole or an echinocandin over AmB because of the observation of in vitro polyene resistance.

For all patients with candidemia, a dilated funduscopic examination sometime within the first week after initiation of therapy and routine blood cultures to document clearance of *Candida* from the bloodstream is strongly advised (see Performance Measures). If there are no metastatic complications, the duration of antifungal therapy is 14 days after resolution of signs and symptoms attributable to infection and clearance of *Candida* species from the bloodstream. This recommendation is based on the results of several prospective, randomized trials in which this rule has been successfully applied, and it is generally associated with few complications and relapses [27, 28, 51–54, 79]. The recommended length of therapy pertains to all systemic antifungal therapy and includes sequential therapy with AmB or an echinocandin followed by an azole.

Central venous catheters should be removed when candidemia is documented, if at all possible [82–84]. The data supporting this are strongest among nonneutropenic patients and show that catheter removal is associated with shorter duration of candidemia [82, 83] and reduced mortality in adults [82, 84] and neonates [85]. Recently completed trials in adults suggest better outcomes and shorter duration of candidemia among patients in whom central venous catheters were removed or replaced [28, 54]. Among neutropenic patients, the role of the gastrointestinal tract as a source for disseminated candidiasis is evident from autopsy studies, but in an individual patient, it is difficult to determine the relative contributions of the gastrointestinal tract versus catheter as primary sources of candidemia [82, 86]. An exception is made for candidemia due to *C. parapsilosis*, which is very frequently associated with catheters [87]. There are no randomized studies on this topic, but the Expert Panel strongly favors catheter removal when feasible. The role for antifungal lock solutions is not well defined.

II. WHAT IS THE TREATMENT OF CANDIDEMIA IN NEUTROPENIC PATIENTS?

Recommendations

9. An echinocandin (caspofungin, loading dose of 70 mg, then 50 mg daily; micafungin, 100 mg daily (A-II); anidulafungin, loading dose of 200 mg, then 100 mg daily (A-III)) or LFAmB (3–5 mg/kg daily) (A-II) is recommended for most patients.

10. For patients who are less critically ill and who have no recent azole exposure, fluconazole (800 mg [12 mg/kg] loading

9. Bir ekinokandin veya LFAmB (A-II).

10. Hafif klinik tabloda ve önceden azol kullanımı olmayan hastada flukonazol (B-III); küflerin de kapsanması düşünülüyorsa vorikonazol (B-III)

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dose, then 400 mg [6 mg/kg] daily) is a reasonable alternative (B-III). Voriconazole (400 mg [6 mg/kg] twice daily for 2 doses, then 200 mg [3 mg/kg] twice daily) can be used in situations in which additional mold coverage is desired (B-III).

11. For infections due to *C. glabrata*, an echinocandin is preferred (B-III). L-AmB is an effective but less attractive alternative because of cost and the potential for toxicity (B-III). For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable (B-III).

12. For infections due to *C. parapsilosis*, fluconazole or LFAmB is preferred as initial therapy (B-III). If the patient is receiving an echinocandin and is clinically stable and if follow-up culture results are negative, continuing use of the echinocandin until completion of therapy is reasonable. For infections due to *C. krusei*, an echinocandin, LFAmB, or voriconazole is recommended (B-III).

13. Recommended duration of therapy for candidemia without persistent fungemia or metastatic complications is 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia and resolution of neutropenia (A-III).

14. Intravenous catheter removal should be considered (B-III).

Evidence Summary

Candidemia in neutropenic patients is a life-threatening infection that is associated with acute disseminated candidiasis, a sepsis-like syndrome, multiorgan failure, and death. Candidemia associated with *C. tropicalis* is particularly virulent in neutropenic hosts. Chronic disseminated candidiasis can ensue as a complication of candidemia in neutropenic patients despite antifungal therapy.

There are no adequately powered randomized controlled trials of treatment of candidemia in neutropenic patients. The data are largely derived from single-arm studies or from small subsets of randomized controlled studies that have enrolled mostly nonneutropenic patients. Historically, candidemia in the neutropenic patient has been treated with an AmB formulation. The availability of voriconazole and the echinocandins have led to greater use of these agents in this clinical scenario but without compelling clinical data. The extensive use of fluconazole for prophylaxis to prevent invasive candidiasis in neutropenic patients and the lack of significant prospective data has led to a diminished therapeutic role for this agent among these patients.

The numbers of neutropenic patients included in recent candidemia treatment studies are small, but response rates are encouraging. In these trials, 50% of caspofungin recipients versus 40% of AmB-d recipients [51], 68% of micafungin recipients versus 61% of L-AmB recipients [52], and 69% of micafungin recipients versus 64% of caspofungin recipients [54] with neutropenia at onset of therapy were successfully treated. Data from the recent randomized controlled trial of anidulafungin versus fluconazole enrolled too few neutropenic patients with candidemia to generate meaningful data regarding efficacy [53]. In 2 retrospective studies, successful outcomes for primary treatment of neutropenic patients were reported in 64% of those receiving AmB-d, 64% of those receiving fluconazole, and 68% of those receiving caspofungin [88, 89].

An extremely important factor influencing the outcome of candidemia in neutropenic patients is the recovery of neutrophils during therapy. In a large retrospective cohort of 476 patients with cancer who had candidemia, persistent neutropenia was associated with a greater chance of treatment failure [87].

Additional insights can be gleaned from data derived from studies of empirical antifungal therapy involving febrile patients with neutropenia who had candidemia at baseline. In these studies, baseline candidemia was cleared in 73% of those treated with AmB-d versus 82% of those treated with L-AmB [90] and in 67% of those treated with caspofungin versus 50% of those treated with L-AmB [91]. Data from a large randomized trial also suggest that voriconazole is a reasonable choice for febrile patients with neutropenia and suspected invasive candidiasis for whom additional mold coverage is desired [92].

On the basis of these limited data, the success rates of antifungal therapy for candidemia in patients with neutropenia do not appear to be substantially different from those reported in the large randomized trials of nonneutropenic patients. Moreover, these data do not suggest less favorable outcomes associated with fluconazole and voriconazole, but many physicians prefer LFAmB or an echinocandin, which may be more fungicidal, as first-line agents. Similar to the approach in nonneutropenic patients, the recommended duration of therapy for candidemia in neutropenic patients is for 14 days after resolution of attributable signs and symptoms and clearance of the bloodstream of *Candida* species, provided that there has been recovery from neutropenia. This recommendation is based on the limited data from prospective randomized trials and has been associated with few complications and relapses [51, 52, 54].

The management of intravascular catheters in neutropenic patients with candidemia is less straightforward than in their nonneutropenic counterparts. Distinguishing gut-associated from vascular catheter–associated candidemia can be difficult in these patients [86], the data for catheter removal is less compelling, and the consequences of catheter removal often create significant intravenous access problems. Nonetheless, the Expert Panel suggests consideration of venous catheter removal (including removal of tunneled catheters) for neutropenic patients who have persistent candidemia and in whom it is logistically feasible.

12. *C. parapsilosis* için Flukonazol veya LFAmB (B-III)
Ekinokandin almakta olan hastada klinik stabil ve sonraki kültürler negatifse tedaviye devam
C. krusei için ekinokandin, LFAmB veya vorikonazol (B-III)

13 ve 14. Tedavi süresi metastatik komplikasyon yoksa kandan kandidaların temizlenmesinden ve semptomların gerilemesinden sonra 2 hafta (A-III)
Kateterin çıkarılması önerilebilir (B-III)

ESCMID PUBLICATIONS 10.1111/1469-0691.12041

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)

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Ampirik Teda

Mifafungin BII
Anidulafungin ?

LAmB ve Kaspofungin AI

FLC CI
AmB-d DII

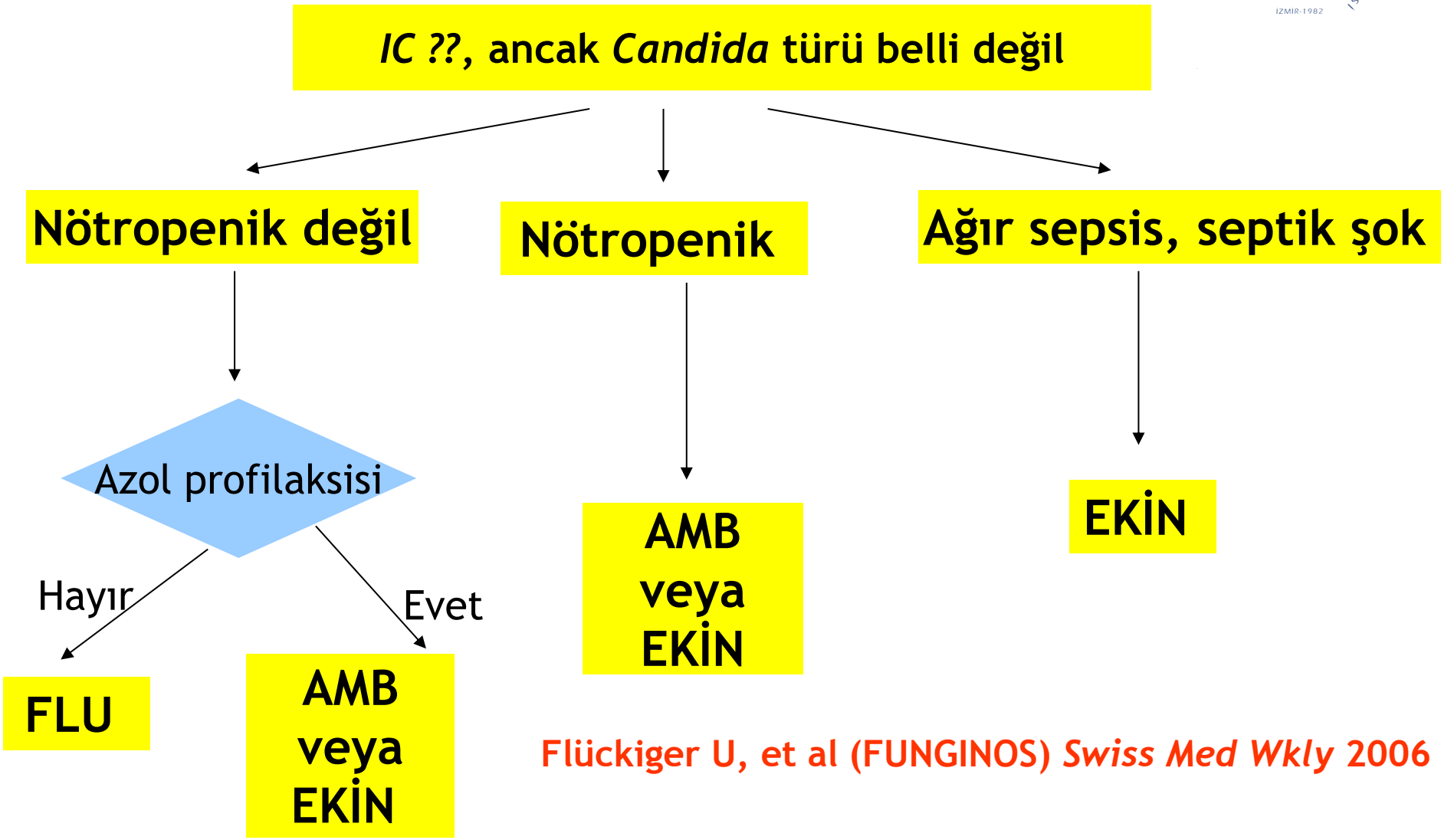
ITC ve VOR BI

TABLE 4. Empiric therap *dida* disease: All situations causing severe and prolonged neutropenia

Intention	Int		A			R
Morbidity reduction	Liposomal amphotericin B (3 mg/kg/day)					[4
	Caspofungin (70 mg on day 1 then 50 mg)					[4
	Amph lidal dispersion (4 mg/kg/day)		Yes		I	[5
	A /kg/day)		Yes		I	[5
	It /day)			B	I	[5
	V §		Yes	B	I	[4
	Fl		ND	C*	I*	[5
	Ar		Yes	D	II_t	[4
	Micafungin (100 mg)		Yes	B	II	[4
	Anidulafungin		ND	NR		N

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

Tedavi Yaklaşımı



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RESEARCH ARTICLE **Open Access**

Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial

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Abstract

Background: Hospitalized patients are at increased risk for candidemia and invasive candidiasis (C/IC). Improved therapeutic regimens with enhanced clinical and pharmacoeconomic outcomes utilizing existing antifungal agents are still needed.

Methods: An open-label, non-comparative study evaluated an intravenous (IV) to oral step-down strategy. Patients with C/IC were treated with IV anidulafungin and after 5 days of IV therapy had the option to step-down to oral azole therapy (fluconazole or voriconazole) if they met prespecified criteria. The primary endpoint was the global response rate (clinical + microbiological) at end of treatment (EOT) in the modified intent-to-treat (MITT) population (at least one dose of anidulafungin plus positive *Candida* within 96 hours of study entry). Secondary endpoints included efficacy at other time points and in predefined patient subpopulations. Patients who stepped down early (≤ 7 days' anidulafungin) were identified as the "early switch" subpopulation.

Results: In total, 282 patients were enrolled, of whom 250 were included in the MITT population. The MITT global response rate at EOT was 83.7% (95% confidence interval, 78.7–88.8). Global response rates at all time points were generally similar in the early switch subpopulation compared with the MITT population. Global response rates were also similar across multiple *Candida* species, including *C. albicans*, *C. glabrata*, and *C. parapsilosis*. The most common treatment-related adverse events were nausea and vomiting (four patients each).

Conclusions: A short course of IV anidulafungin, followed by early step-down to oral azole therapy, is an effective and well-tolerated approach for the treatment of C/IC.

Trial registration: ClinicalTrials.gov: NCT00496197

Keywords: Anidulafungin, Azole, Candidemia, Step-down strategy

Timsit *et al. Trials* 2013, **14**:399
http://www.trialsjournal.com/content/14/1/399

TRIALS

STUDY PROTOCOL Open Access

EMPIRICUS micafungin versus placebo during nosocomial sepsis in Candida multi-colonized ICU patients with multiple organ failures: study protocol for a randomized controlled trial

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Abstract

Background: The potential interest of antifungal treatment of non-immunocompromized patients with sepsis, extra-digestive *Candida* colonization and multiple organ failure is unknown. It represents three-quarters of antifungals prescribed in Intensive Care Units. It may allow early treatment of invasive fungal infection in the incubation phase but expose patients to unnecessary antifungal treatments with subsequent cost and fungal selection pressure. As early diagnostic tests for invasive candidiasis are still considered to be insufficient, the potential interest in this strategy needs to be demonstrated.

Methods: This prospective multicenter, double blind, randomized-controlled trial is conducted in 23 French Intensive Care Units. All adult patients, mechanically ventilated for more than four days with sepsis of unknown origin and with at least one extradigestive fungal colonization site and multiple organ failure are eligible for randomization. Patients with proven invasive candidiasis are not included. After a complete mycological screening, patients are allocated to receive micafungin 100 mg intravenously once a day or placebo for 14 days. We plan to enroll 260 patients. The main objective is to demonstrate that micafungin increases survival of patients without invasive candidiasis at day 28 as compared to placebo. Other outcomes include day 28 and 90 survival and organ failure evolution. Additionally, pharmacokinetics of micafungin in enrolled patients will be measured and evolution of fungal biomarkers and susceptibility profiles of infecting fungi will also be followed.

Discussion: This study will help to provide guidelines for treating non-immunocompromized patients with fungal colonization multiple organ failure and sepsis of unknown origin.

Trial registration: Clinicaltrials.gov number NCT01773876

Keywords: Colonization, Nosocomial sepsis, Candidemia, Invasive candidiasis, Micafungin

Eve Dönerken Yolluk

- IC nadir bir infeksiyon değil
- Her merkez kendi epidemiyolojisini bilmeli
- Erken tedavi mortaliteyi azaltır
- Tanı yöntemlerinin duyarlılığı az
- Farkındalık gerekli

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