Febril Nötropenide Antifungal Profilaksi ve Tedavi

Dr. Bilgin ARDA
Ege Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

FUNGAL

LER

MAYA

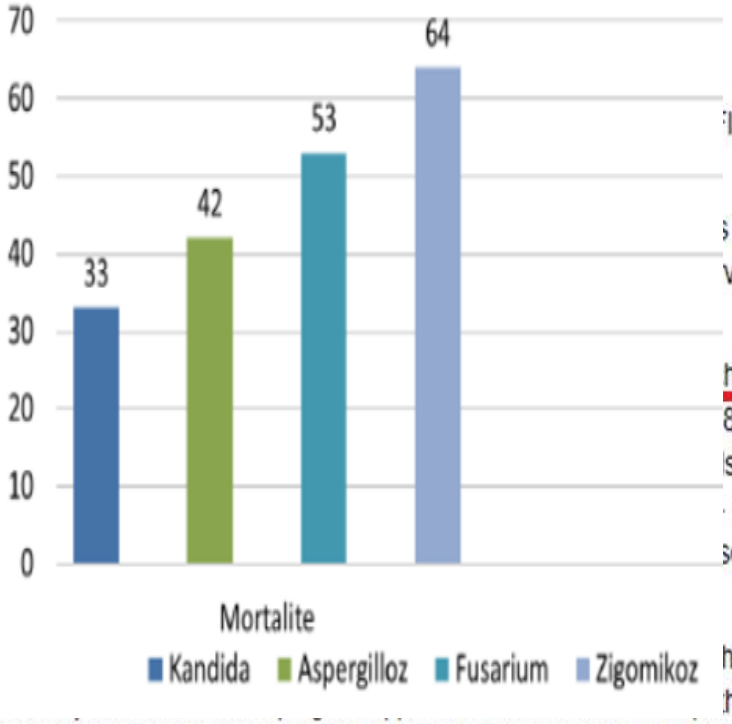
- Candida
  - Albic
  - No
- Cryptoc
- Trichos
- M.furfu

Infections caused by	No. of cases (%)	Incidence %
Molds (%53 A. fumigatus)	**346 (100)**	**2.9**
Aspergillus spp.	310 (90)	2.6
Zygomycetes	14 (4)	
Fusarium spp.	15 (4)	
Others*	7 (2)	
Yeasts (%57 non-albicans)	**192 (100)**	
Candida spp.	175 (91)	
Cryptococcus spp.	8 (4)	
Trichosporon spp.	7 (4)	
Others°	2 (1)	

**Scedosporium spp. (n=3), Acremonium spp. (n=2), Penicillium spp. (n=1); °Rhodotorula spp 1, Hansenul*

gic malignancies: the SEIFEM-

hini A, Fanci R, Caramatti C, Invernizzi R, Mattei D,



- Olgular
(538)
fungal er
görü
- %69'u
- Küf (34
%2,5
- Maya (192/538)
%1,6

ere 2% (209/11802) and 39% (20
owed by fusariosis (53%), aspergil

NCLUSIONS: Patients with hemat
IFI is highest among patients with
ther agents are rare. The attributable mortality rate for aspergillosis has dropped from 60-70% to approximately
40%. Candidemia-related mortality remains within the 30-40% range reported in literature although the incidence has decreased.

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Journal of Infection (1996) 33, 23–32

Trends in the Postmortem Epidemiology of Invasive Fungal Infections at a University Hospital

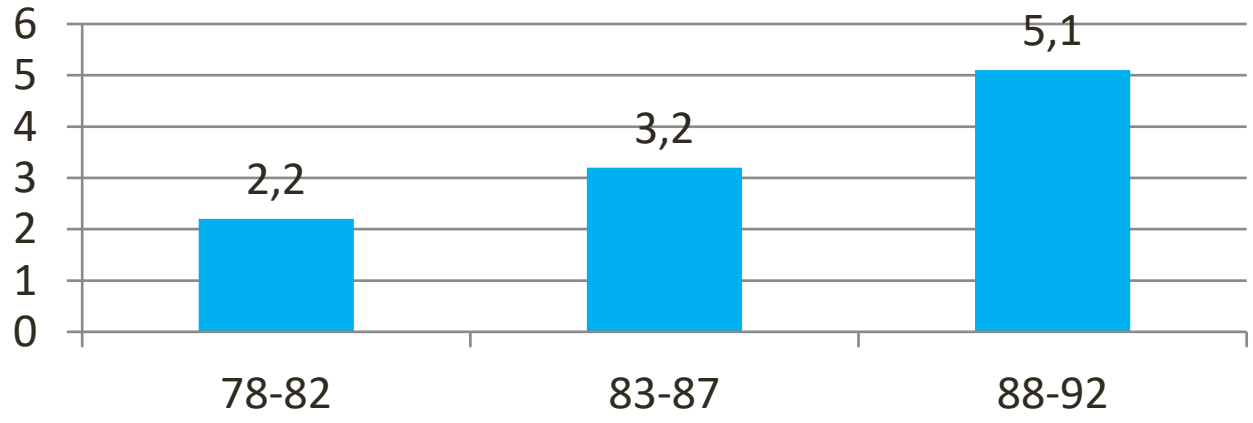
A. H. Groll*†, P. M. Shah, C. Mentzel, M. Schneider, G. Just-Nuebling and K. Huebner

Department of Pathology and Department of Medicine, Johann Wolfgang Goethe University Hospital, Frankfurt/Main, Germany

- Almanya (1978-1992)

8124 otopsi

278 (%3,4) İFİ



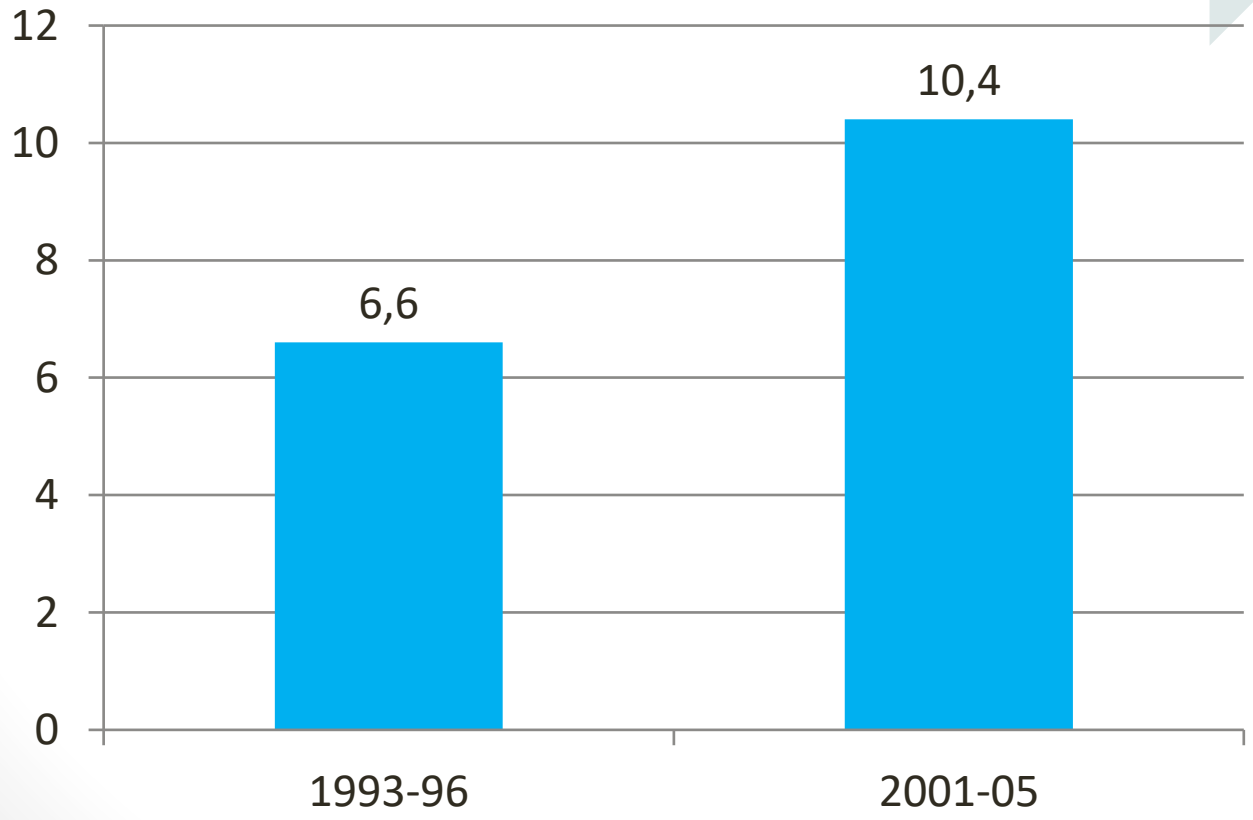
Trends in the postmortem epidemiology of invasive fungal infections at a university hospital☆

T. Lehrnbecher [a,*], C. Frank [a], K. Engels [b], S. Kriener [b], A.H. Groll [c], D. Schwabe [a]

- Almanya (1993-2005)

2707 otopsi

221 (%8,2) İFİ



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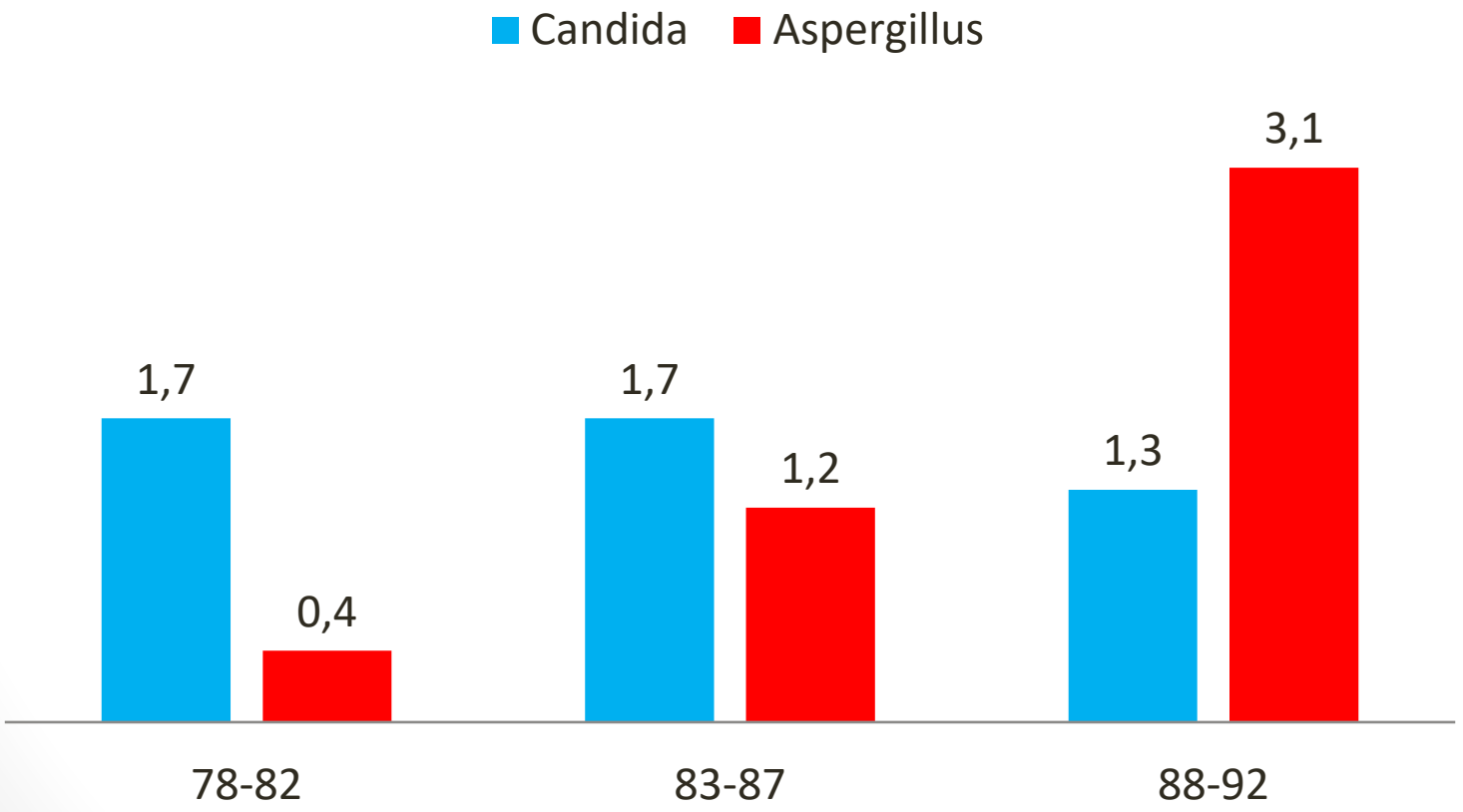


DOĞAL İMMÜN SİSTEM

Toll-benzeri reseptör polimorfizmi
C-tip lektin reseptör polimorfizm
Mannoz bağlayan lektin polimorfizmi
Plazminojen polimorfizmi
Diğer polimorfizimler?

ALTTA YATAN DURUMA BAĞLI FAKTÖRLER

Nötropeni
İlerleyen kanser
« Graft versus host « hastalığı
Kanser kemoterapisi
Steroidler,
T-hücre baskılayan tedaviler

PRİMER KONAK FAKTÖRLERİ

Hematolojik malignite
AKHN
Solid organ nakli
Solid tümör
Diğer immün yetmezlikler

İklim
İnşaat
Yaşanan yer
Tütün ve kenevir kullanımı
Kontamine yiyecek ve biberler
Evcil hayvanlar, bahçe işleri ile uğraşmak, saksı bitkileri
Hastane yatışı sırasında HEPA filtresi olmayan ortamda tedavi görmek

ÇEVRESEL FAKTÖRLER

Diabetes mellitus
Aşırı Demir Yükü
Travma
Yanık
Böbrek yetmezliği
Metabolik asidoz
Daha önceden olan akciğer hastalığı

DİĞER FAKTÖRLER

Herbrecht et al., Ann NY Acad Sci 2012

Riskli Hasta Grupları

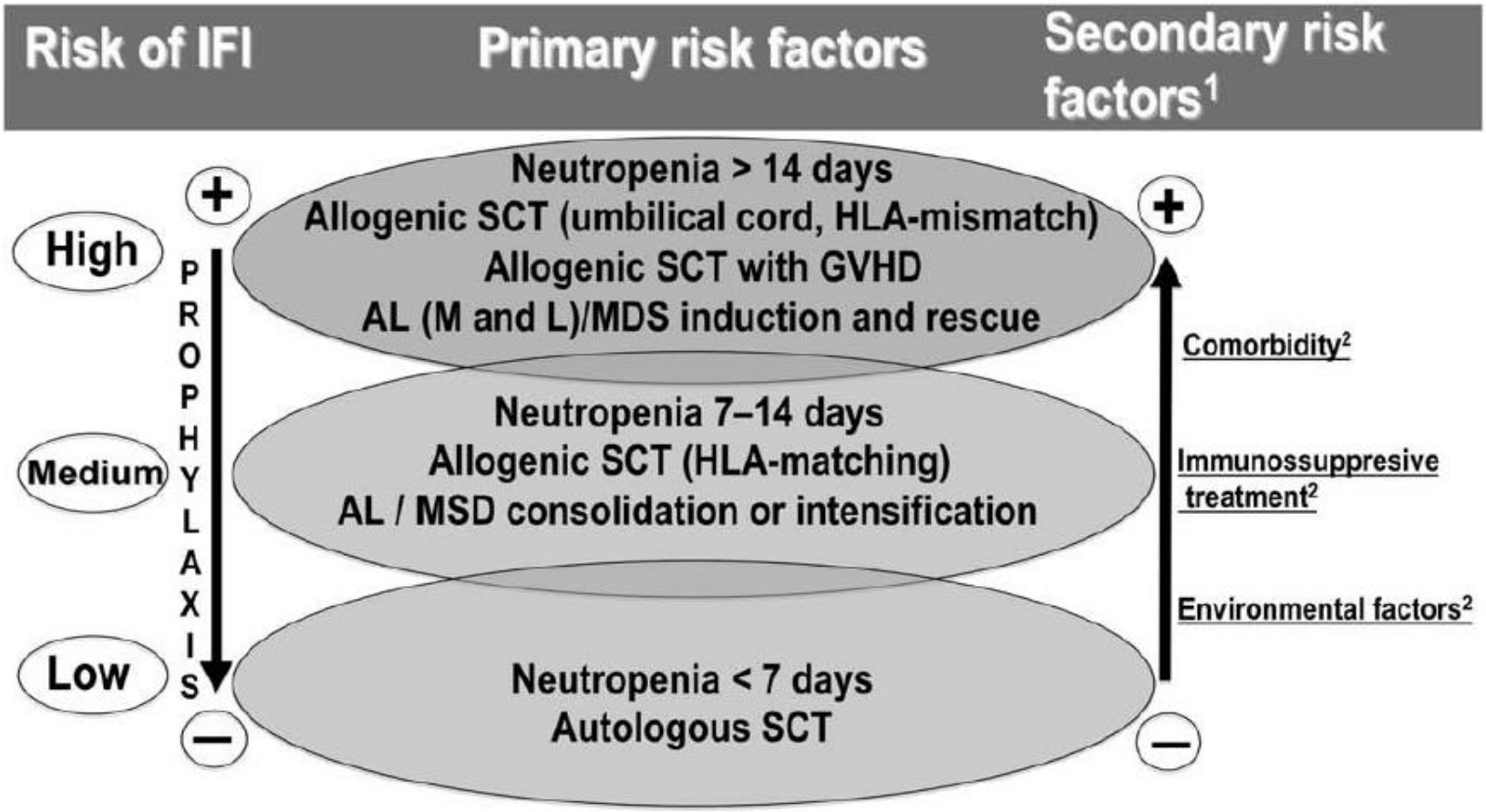
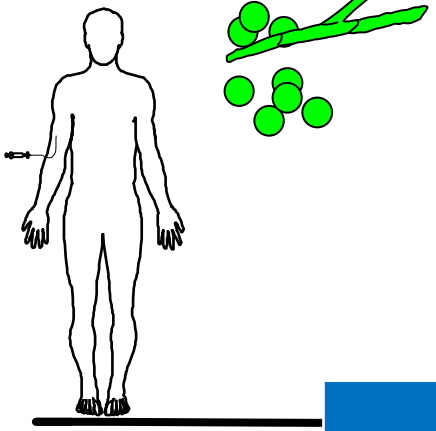


Figure 1 | Classification of the risk groups for IFI.

IFI Tedavi Stratejileri

- ✓ Yüksek riskli Hasta
- ✓ Yüksek riskli dönem

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



Hastalık yükü

Kaba mortalite
60% to 90%

İNFEKSİYON ODAĞI/YÜKSEK OLASI

TANISAL BAZLI TEDAVİ

Ampirik AFT

+CT/GM

POZİTİF KÜLTÜR

Hastalık yok

Profilaksi

dite/
rtalite

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

Journal of Fungi

MDPI

Review

Development and Applications of Prognostic Risk Models in the Management of Invasive Mold Disease

Marta Stanzani [1] and Russell E. Lewis [2,*]

Altta yatan hastalık

Nötropeni

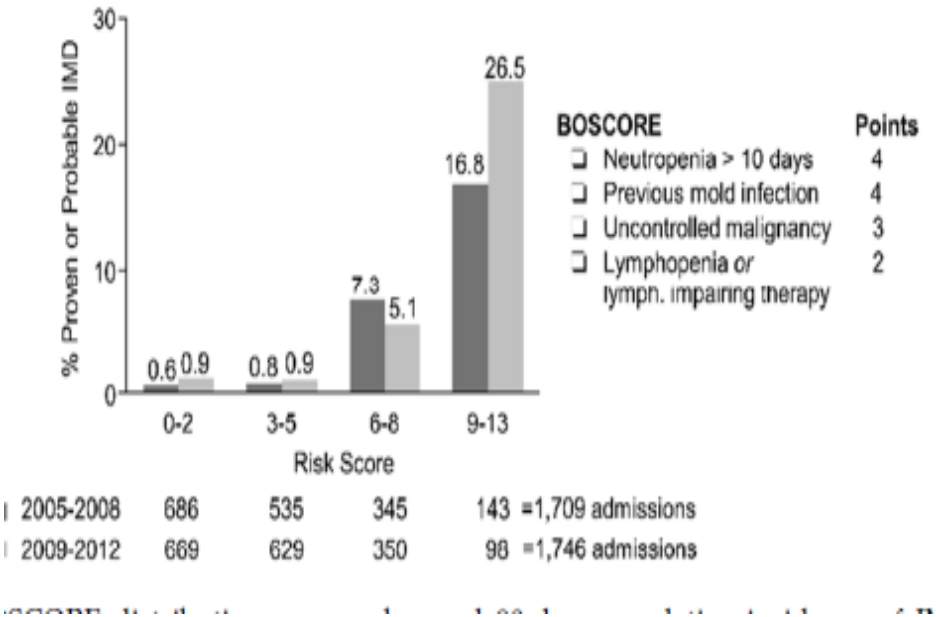
İmmünsüpresif rejim

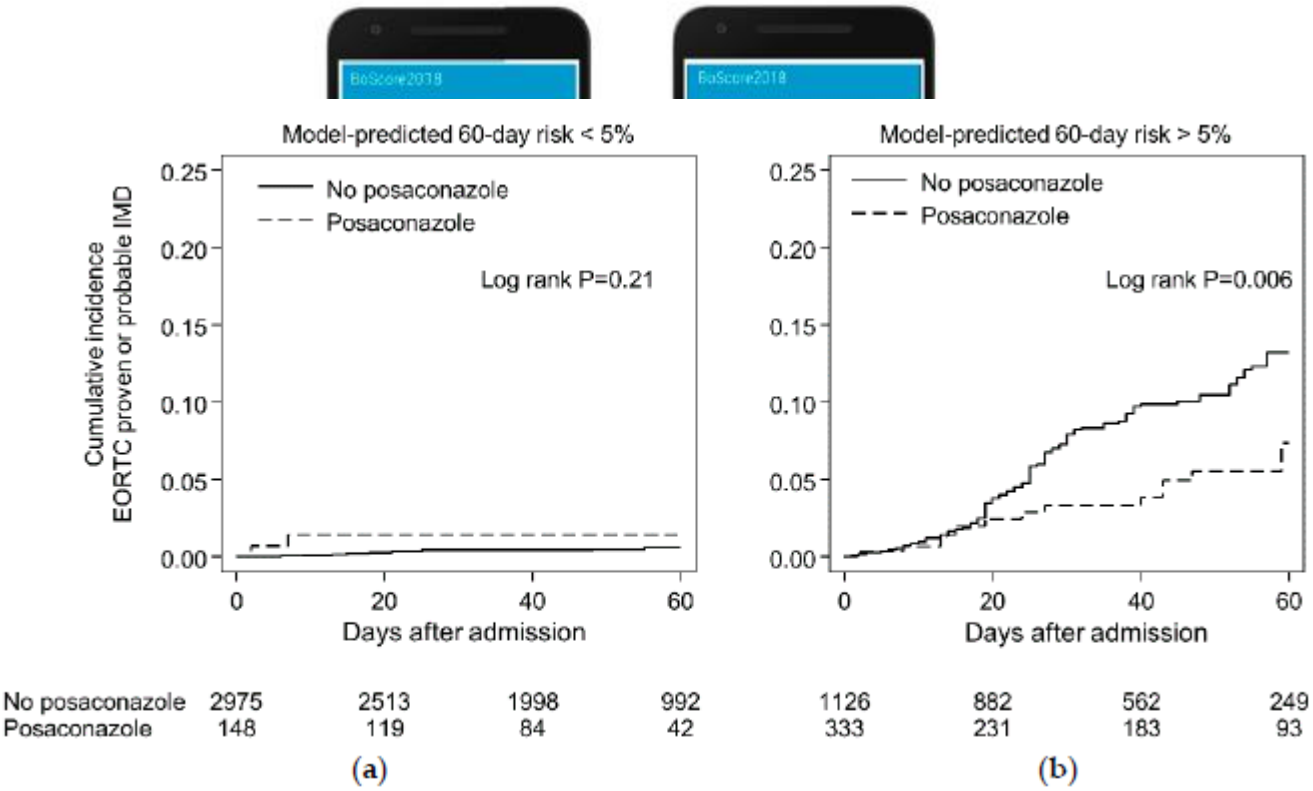
KİT

Çevresel faktörler

Komorbidite

….





neutropenia) + (1.64 × previous mold disease) − 5.45. To calculate the 60-day probability from the formula, the calculated result is first converted from log odds to odds (eRisk); then odds must be

ANTIMICROBIAL PROPHYLAXIS BASED ON OVERALL INFECTION RISK IN PATIENTS WITH CANCER

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Antimicrobial Prophylaxis[d]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 days	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - [illegible] • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia › Induction › Consolidation/maintenance • Alemtuzumab therapy • Moderate to severe GVHD • Anticipated neutropenia greater than 10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - [illegible] • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

Mukozit varsa nötropeni süresince AF profilaksi

nötropeni süresince AF profilaksi

KEY: CLL = chronic lymphocytic leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus, PJP: Pneumocystis *jirovecii* pneumonia

PREVENTION OF FUNGAL INFECTIONS

See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Antifungal Prophylaxis See Antipneumocystis Prophylaxis (INF-6)	Duration
Intermediate to High	ALL	Consider: • Fluconazole[g] or an echinocandin[h] • Amphotericin B products[i] (category 2B)	
	MDS (neutropenic) AML (neutropenic)	Consider: • Posaconazole[g] (category 1) • Voriconazole,[g] fluconazole,[g] an echinocandin,[h] or amphotericin B products[i] (all category 2B)	Typically until resolution of neutropenia
	Autologous HCT with mucositis[f]	Consider: • Fluconazole[g] or an echinocandin[h] (both category 1)	
	Autologous HCT without mucositis	Consider no prophylaxis (category 2B)	N/A
	Allogeneic HCT (neutropenic)	Consider: • Fluconazole[g] or an echinocandin[h] (both category 1) • Voriconazole,[g] posaconazole,[g] or amphotericin B products[i] (all category 2B)	Continue during neutropenia[j]
	Significant GVHD receiving immunosuppressive therapy	Consider: • Posaconazole[g] (category 1) • Voriconazole,[g] echinocandin, or amphotericin B products[i] (all category 2B)	Until resolution of significant GVHD

KEY: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, MDS = myelodysplastic syndromes

Flukonazol ve Posakonazol

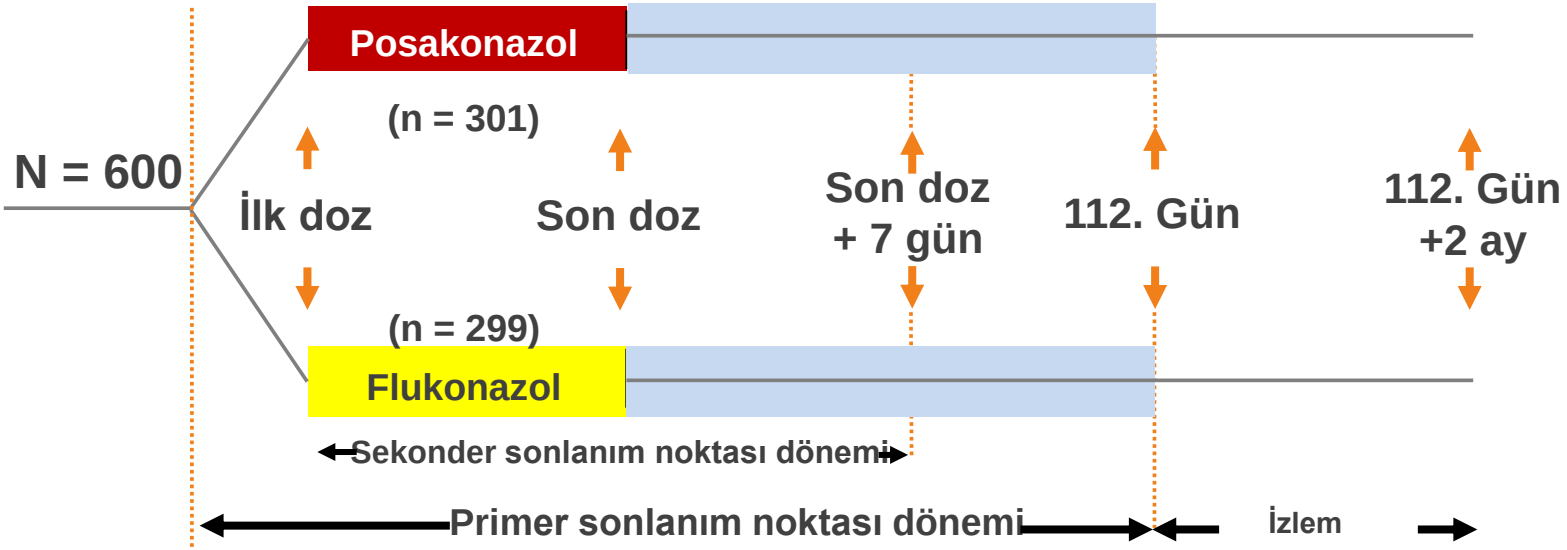
GVHH

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

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

Flukonazol ve Posakonazol

GVHH

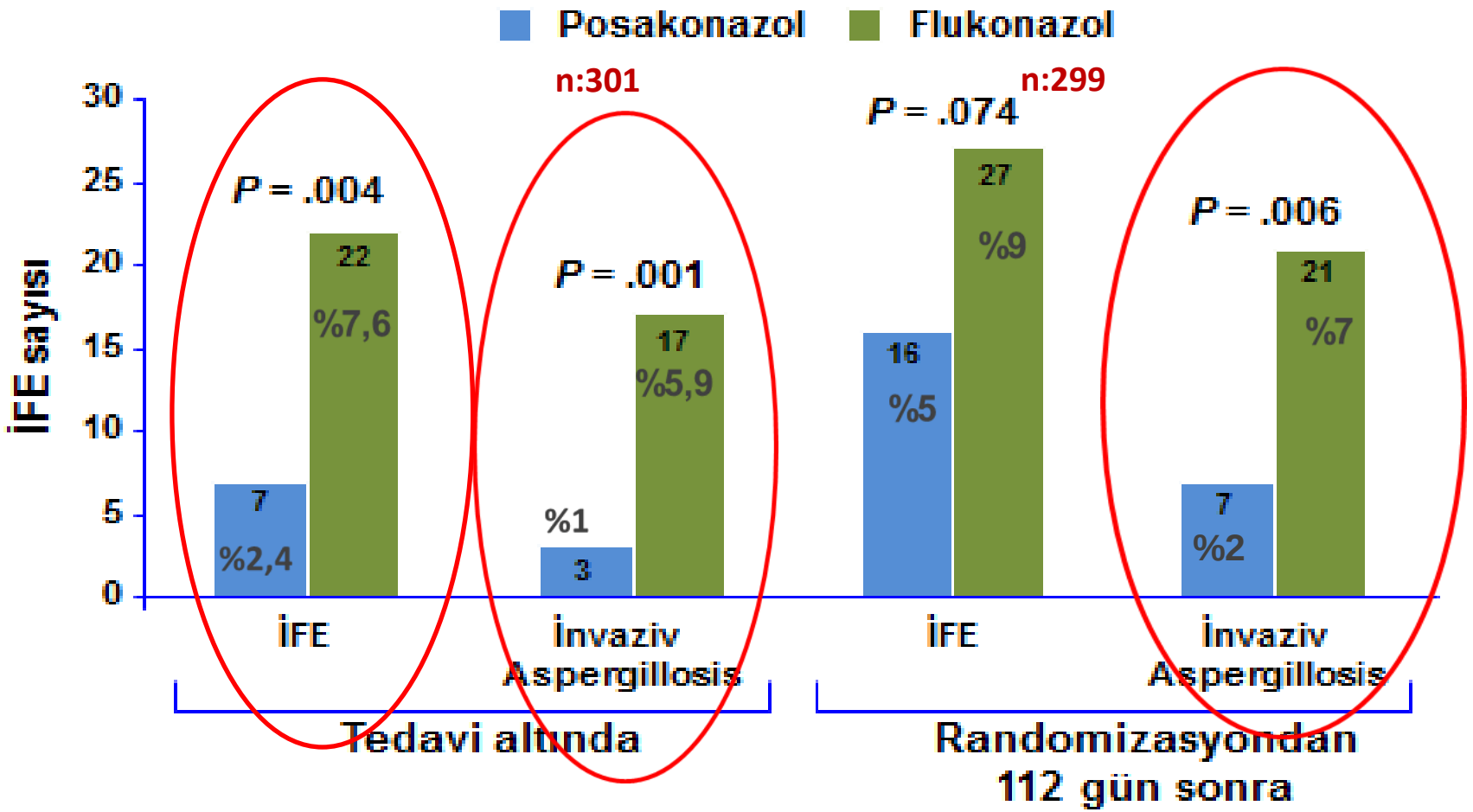


Sabit tedavi dönemi (sabit dönem): çalışma dönemi, 112 gün (primer sonlanım noktası dönemi).

Maruziyet dönemi (tedavi dönemi): çalışma ilacının ilk dozunun alınmasından son dozdan 7 gün sonrasına kadar (sekonder sonlanım noktası dönemi).

Andrew J. Ullmann. N Engl J Med. 2007;356:335-347

Kanıtlanmış/yüksek olasılıklı İFE insidansı



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

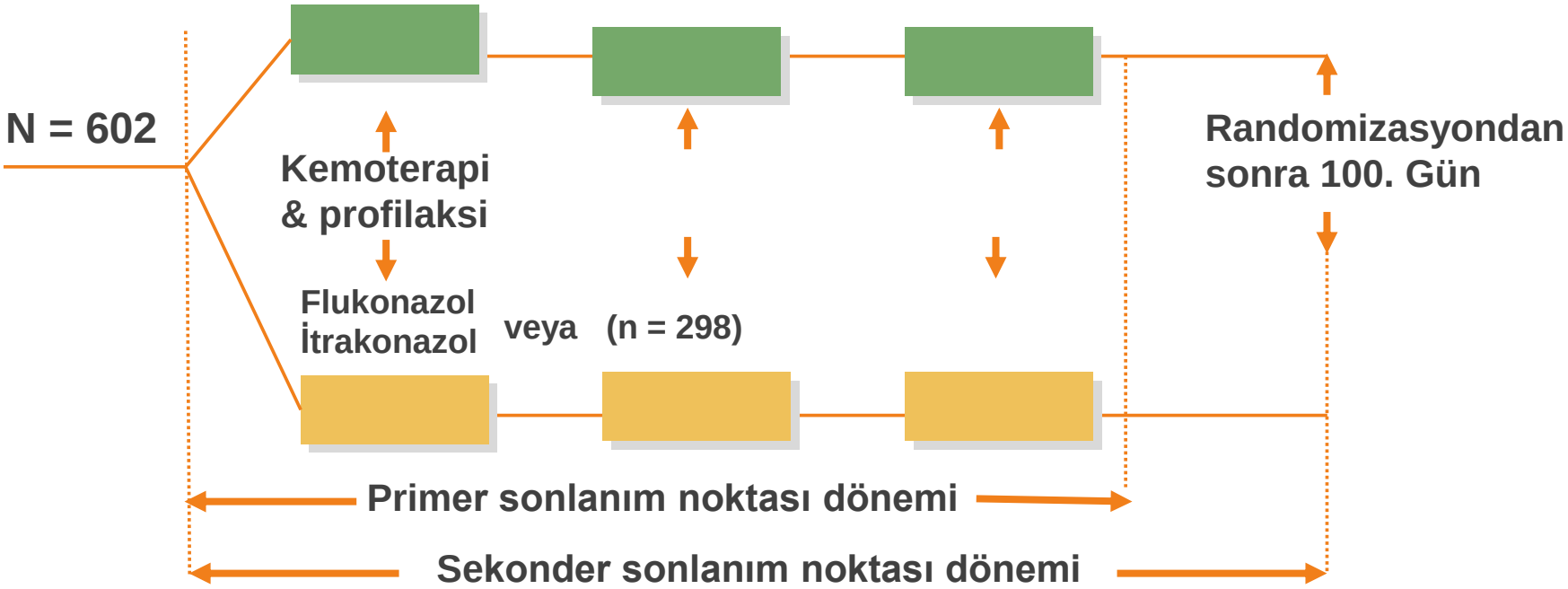
Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and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

Flukonazol/İtrakonazol ve Posakonazol

AML/MDS

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

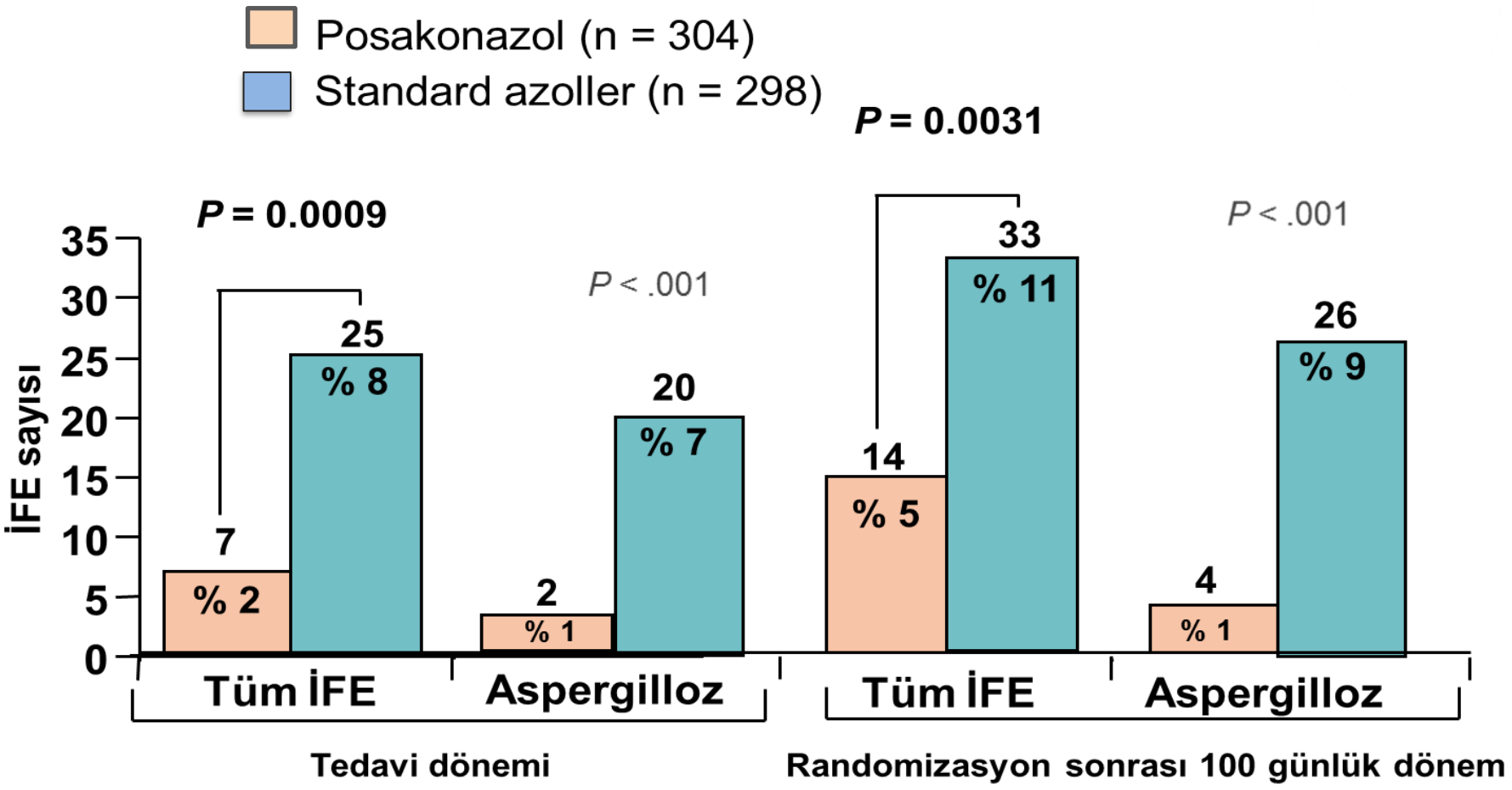
Yüksek riskli AML/MDS hastalarında flukonazol/ itrakonazol profilaksisi ile posakonazol profilaksisinin karşılaştırılması



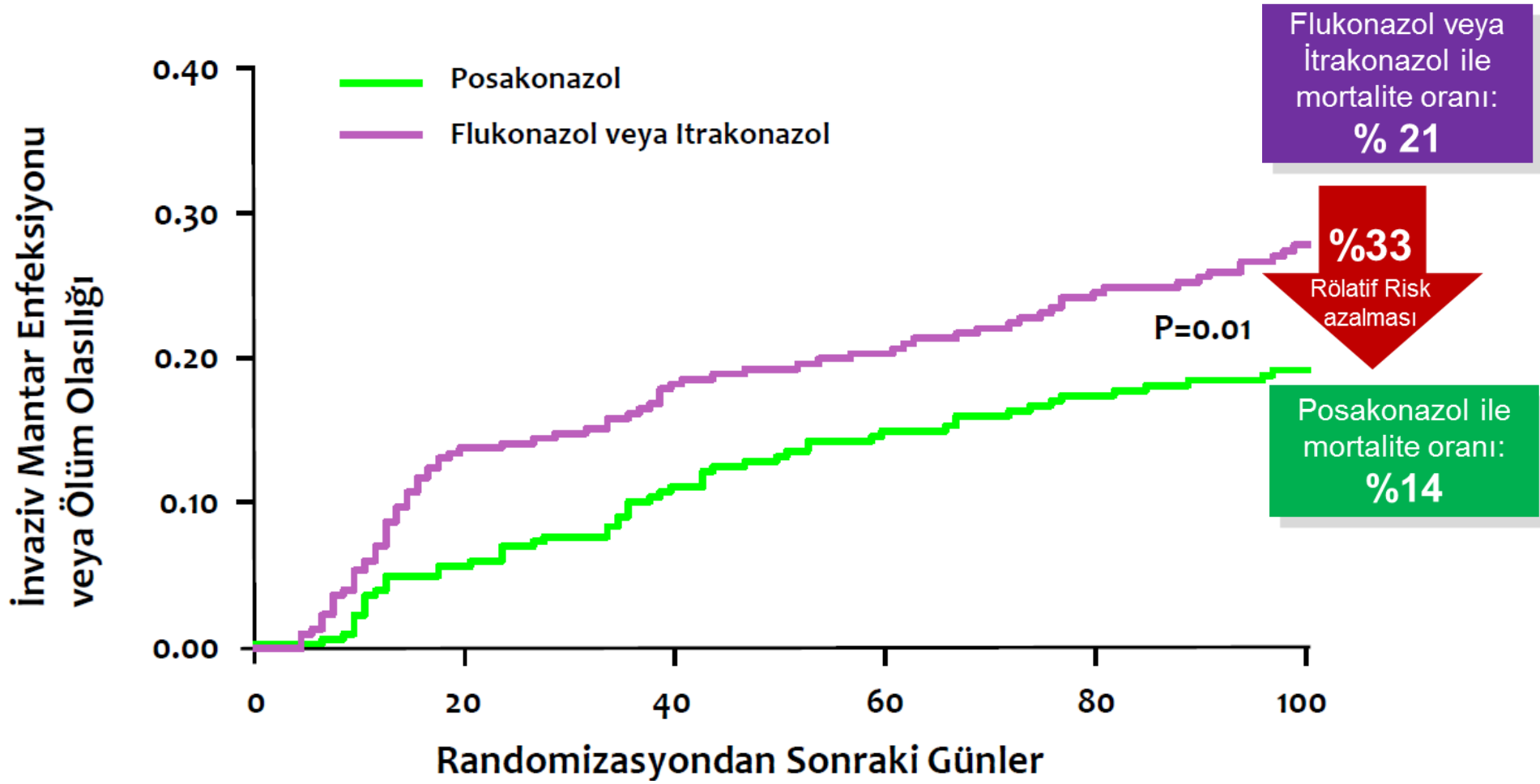
Tedavi dönemi: Randomizasyondan itibaren son dozdan sonra 7. güne kadar (primer sonlanım noktası)

Randomizasyondan sonra 100 günlük dönem (sekonder sonlanım noktası)

Cornely OA et al. N Engl J Med. 2007;356:348-359



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



AML hastalarında profilaksi ile genel mortalitede azalma

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

Primer profilaksi

- AML/MDS indüksiyon tedavisi, uzamış ve derin nötropenide

Posakonazol 200mg süsp günde 3 kez
300mg tb günde 1 kez **(A-I)**

L-AmB 12.5 mg, inhaler, haftada 2 kere + flukonazol (dozu net değil) **(B-I)**

ABLC 3mg/kg, haftada 3 kere
Mikafungin 50mg 1x1
L-AmB 10mg/kg q7d
L-AmB 5mg/kg q2d
L-AmB 15mg/kg q14d
Vorikonazol

C-II

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

Primer profilaksi

- Allojenik kök hücre nakilli hastalar nötropeniden çıkana kadar

  Posakonazol 200mg süsp günde 3 kez

  300mg tb günde 1 kez **(B-II)**

  L-AmB 12.5 mg, inhaler, haftada 2 kere + flukonazol **(B-II)**

  Vorikonazol 200mg 2x1 ve mikafungin 50mg/gün **(C-I)**

➢ Orta/ağır GVHD, yoğunlaştırılmış immunsupresyon durumunda;

  Posakonazol 200mg süsp günde 3 kez

  300mg tb günde 1 kez **(A-I)**

  Vorikonazol 200mg 2x1 **(C-I)**

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

Transplantation and Cellular Therapy
journal homepage: www.tctjournal.org
ASTCT American Society for Transplantation and Cellular Therapy

Guideline

American Society of Transplantation and Cellular Therapy Series. 2: Management and Prevention of Aspergillosis in Hematopoiet Transplantation Recipients

Sanjeet S. Dadwal[1,*], Tobias M. Hohl[2], Cynthia E. Fisher[3], Michael Boeckh[4], Ge Paul A. Carpenter[5], Brian T. Fisher[6], Monica A. Slavin[7], D.P. Kontoyiannis[8]

Article history:
Received 6 October 2020
Accepted 7 October 2020

- Otolog KİT İA riski düşüktür. Candida profilaksisi (Flukonazol, mikafungin) nötrophil sayış (1000 cells/mm3) olana kadar önerilir. AII
- Allojenik KİT nötrofil engrafmanı olana kadar ilk 75 gün İA riski düşüktür Candida spp profilaksisi (fluconazole, micafungin) AII
- Allojenik KİT + GVHD, posaconazole profilaksisi AI
- Vorikonazol posokonazole alternatiftir. BI
- Küf aktif profilaksi alanlarda GM negatifliği İA tanısını dışlamaz. AII
- BAL da Beta D glukan testi spesifitesi düşük rutin önerilmez. DII

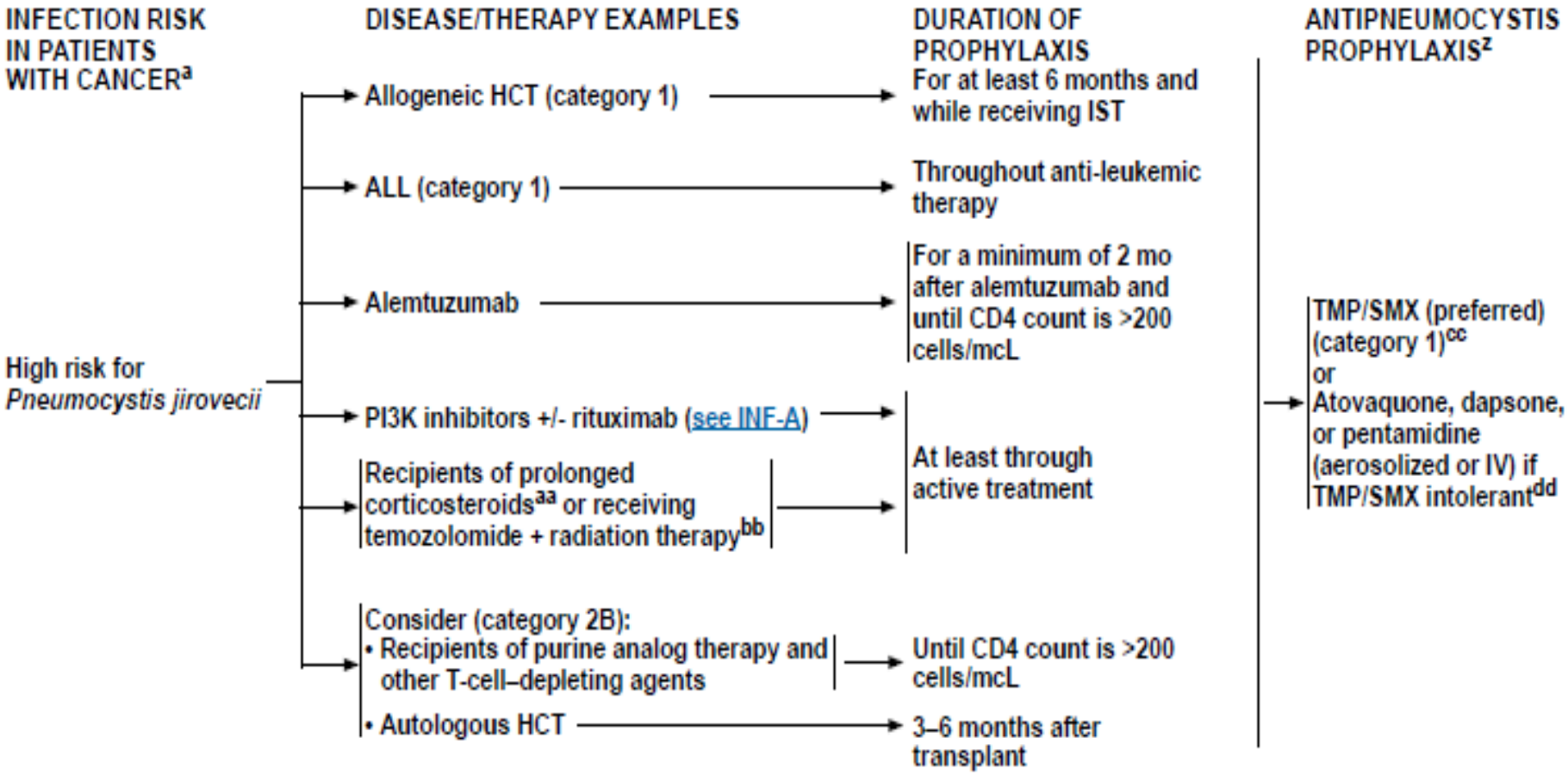
Pneumocystis jirovecii profilaksisi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

PREVENTION OF *PNEUMOCYSTIS JIROVECII (PNEUMOCYSTIS CARINII)* INFECTION



Ampirik AF Tedavi

Ampirik Antifungal Tedavi

Ampirik antifungal tedavi

- Dört-yedi gün antibiyotik uygulanmasına rağmen ateşi devam eden yüksek riskli hastalarda invazif mantar infeksiyonlarının araştırılması ve ampirik antifungal tedavi düşünülmelidir **(AI)**

- Amphoterisin B, Ekinokandin seçilebilir

- Öncesinde küflere karşı etkili bir profilaksi alanlar için intravenöz yolla verilen farklı bir antifungal sınıfına geçiş değerlendirilmelidir **(BIII)**

D–Index–Guided Early Antifungal Therapy Versus Empiric Antifungal Therapy for Persistent Febrile Neutropenia: A Randomized Controlled Noninferiority Trial

Article *in* Journal of Clinical Oncology · January 2020
DOI: 10.1200/JCO.19.01916

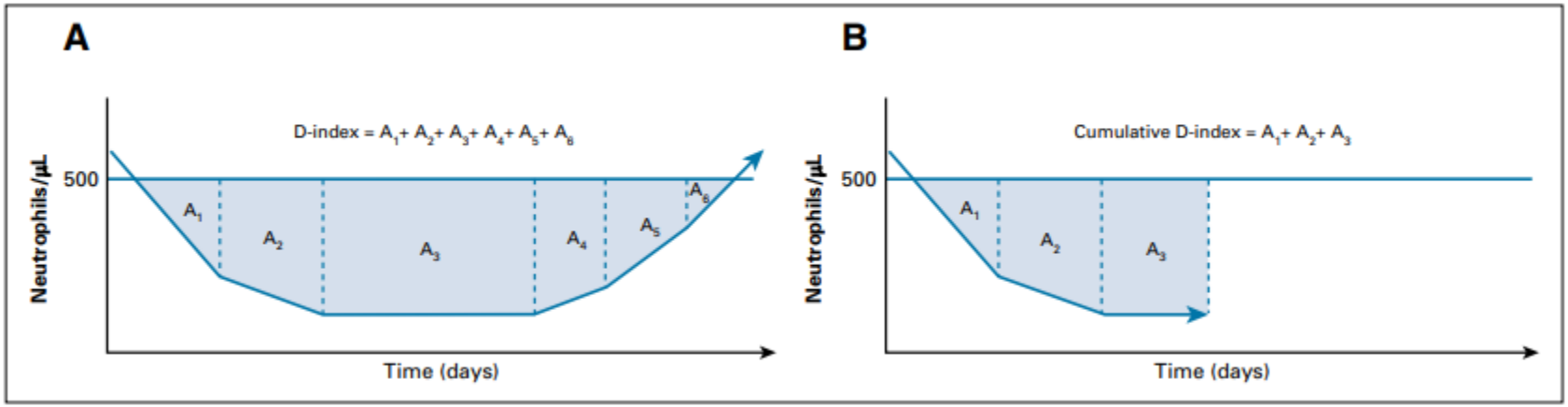


FIG 1. Calculation of the (A) D-index and (B) cumulative D-index.

Aspergillus galactomannan
beta-D-glucan test
Akciğer grafisi
} haftada bir

Gereğinde toraks BT

Kümülatif indeks 5500 ⇧ AF tedavi

Characteristic	DET (n = 212)	EAT (n = 201)
None	207	189
Possible	4	7
Probable	0	4
Proven	1	1
İFİ	%2.4	%6

VORICONAZOLE COMPARED WITH LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL ANTIFUNGAL THERAPY IN PATIENTS WITH NEUTROPENIA AND PERSISTENT FEVER

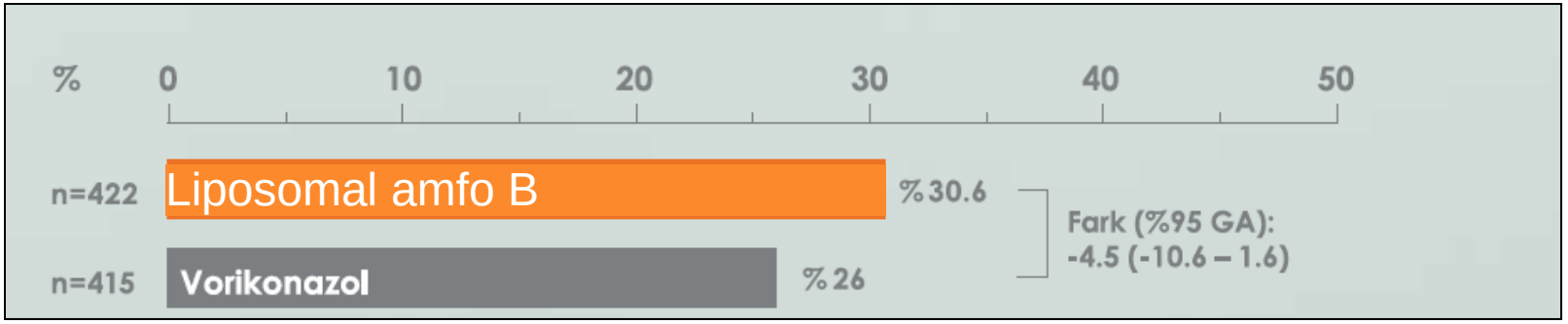
THOMAS J. WALSH, M.D., PETER PAPPAS, M.D., DREW J. WINSTON, M.D., HILLARD M. LAZARUS, M.D., FINN PETERSEN, M.D., JOHN RAFFALLI, M.D., SAUL YANOVICH, M.D., PATRICK STIFF, M.D., RICHARD GREENBERG, M.D., GERALD DONOWITZ, M.D., AND JEANETTE LEE, PH.D., FOR THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP*

Walsh et al, NEJM, 2002

Liposomal Amfoterisin B vs Vorikonazol

Persistan ateş ve nötropenisi olan erişkin hastalarda Liposomal Amfo B ile toplam başarı oranı %30.6'dır.[1]

Persistan ateşi ve nötropenisi olan hastalarda toplam başarı oranları (%)[1]



Persistan ateşi ve nötropenisi olan erişkin hastalarda yapılan AmBisome® ve vorikonazolün tedavi başarısının değerlendirildiği açık-etiketli, prospektif, randomize, çok-merkezli çalışma (n=837). Ortalama yaş vorikonazol grubu için 46.3 ve AmBisome® grubu için 45.0'dır. Vorikonazol iv, birinci gün yükleme dozu olarak 12 satte bir 6 mg/kg iki doz ve ardından 12 saatte bir 3 mg/kg bir idame dozu şeklinde devam edilmiştir (ya da 12 saatte bir 200 mg, ardından en az üç günlük intravenöz tedavi). AmBisome® iv günde 3 mg/kg dozunda başlanmış ve devam edilmiştir. Fungal enfeksiyon kanıtları için protokolde tanımlanan kılavuzlara uyulduğunda, araştırıcıların vorikonazol dozunu 12 saatte bir iv 4 mg / kg ya da 12 saatte bir oral 300 mg.'ye ve AmBisome® dozunu günlük iv 6 mg/kg.'ye artırmasına izin verilmiştir. Toksik etkiler ortaya çıkarsa, AmBisome® dozunu günde 1.5 mg/kg'a düşürmeye izin verilmiştir. Grafik referanstan uyarlanmıştır.

Vorikonazol, non-inferiorite için alt sınıra (-10.0) ulaşamamıştır[1] ve bu yüzden ampirik tedavi için onay alamamıştır.[2]

1.Walsh TJ et al. N Engl J Med 2002;346(4):225-234.
2.Petrikkos G, Skiada A. International Journal of Antimicrobial Agents. 2007; 30:108-117.

Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

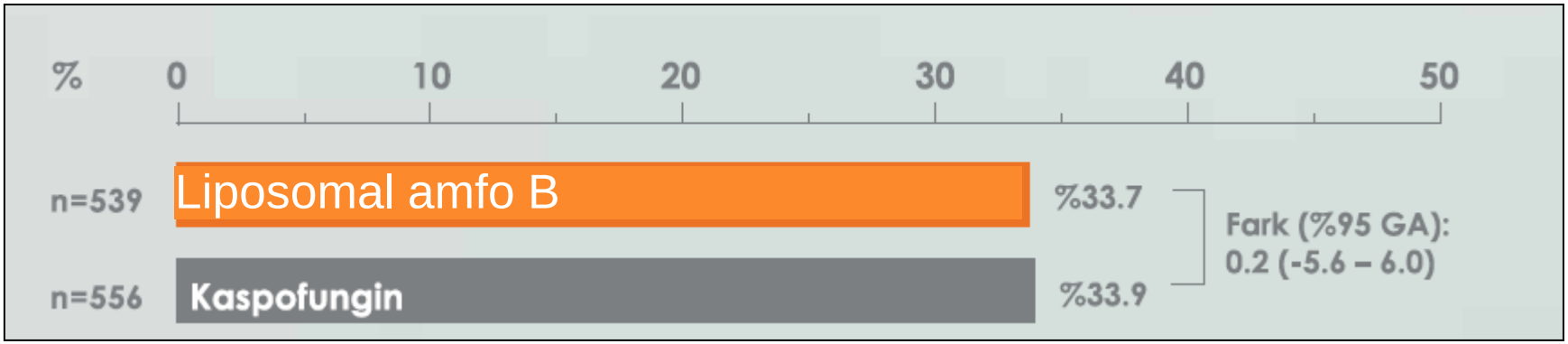
Thomas J. Walsh, M.D., Hedy Teppler, M.D., Gerald R. Donowitz, M.D., Johan A. Maertens, M.D.,

Walsh et al, NEJM, 2004

Liposomal Amfoterisin B vs Caspofungin

L-AmB vs Caspofungin:
Walsh ve ark, 2004

Başarı oranları[1]



Liposomal Amfoterisin B ve Kaspofungin ile benzer başarı oranları.[1]

1.Walsh TJ et al. N Engl J Med 2004;351(14):1391-1402.

Ampirik ya da Pre-empitif Antifungal Tedavi

Ampirik antifungal tedavi

- Dört-yedi gün antibiyotik uygulanmasına rağmen ateşi devam eden yüksek riskli hastalarda invazif mantar infeksiyonlarının araştırılması ve ampirik antifungal tedavi düşünülmelidir **(AI)**

- Liposomal Amphoterisin B, Ekinokandin seçilebilir

- Öncesinde küflere karşı etkili bir profilaksi alanlar için intravenöz yolla verilen farklı bir antifungal sınıfına geçiş değerlendirilmelidir **(BIII)**

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

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Ampirik tedavi mortalite ve morbiditeyi azaltıyor

- Akut lösemi indüksiyon, remisyon KT
- MDS
- KİT

Ateş yok
Aktif enfeksiyon yok
İnfiltrasyon yok
Nötropeni düzelmiş

AF tedaviyi sonlandır

Annals of Hematology
November 2017, Volume 96, Issue 11, pp 1775–1792 | Cite as

Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

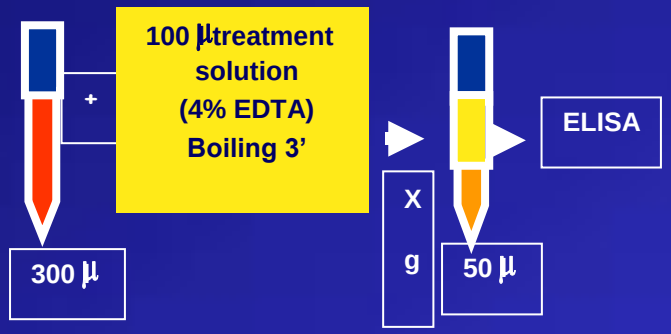
Recommendations for empirical antifungal therapy in high-risk neutropenic patients without prior *Aspergillus*-active antifungal prophylaxis and fever persisting for ≥ 96 h

	Level	Evidence
cAmB	D	I
ABLC	D	I
ABCD	D	I
L-AmB	A	I
Caspofungin	A	I
Itraconazole IV	C	I
Micafungin	C	I
Voriconazole	B	I

Preemtif tedavi

- Ampirik tedavi endikasyonu %40-50
- Gerçek İFİ %10-15
  - Gereksiz tedavi
  - Toksisite
  - Maliyet

Mikoloji- Radyoloji



OLASI

RADYOLOJİ:

Dansite,

Düzgün sınırlı lezon ± halo veya hava-hilal belirtisi veya kavite

YÜKSEK OLASI

MİKOLOJİ + RADYOLOJİ:

Dansite,

Düzgün sınırlı lezon ± halo veya hava-hilal belirtisi veya kavite

KANITLANMIŞ /YÜKSEK OLASILIKLI IFI GM vs BETAGLUKAN

Pazos C, J Clin Microb 2005

	Duyarlılık	Özgüllük	PPV	NPV
Beta-Glukan	88	90	70	96
GM	88	90	70	96
Kombine analiz	88	100	100	96

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Guideline

Article history:
Received 6 October 2020
Accepted 7 October 2020

American Society of Transplantation and Cellular Therapy Series, 2: Management and Prevention of Aspergillosis in Hematopoietic Cell Transplantation Recipients

Sanjeet S. Dadwal[1,*], Tobias M. Hohl[2], Cynthia E. Fisher[3], Michael Boeckh[4], Genofeva Papanicolaou[2], Paul A. Carpenter[5], Brian T. Fisher[6], Monica A. Slavin[7], D.P. Kontoyiannis[8]

Sample	AGM index cutoff
Single serum or plasma	≥1.0
BAL fluid*	≥1.0
Single serum when concomitant BAL fluid AGM ≥0.8	≥0.7
BAL fluid when concomitant serum or plasma ≥0.7	≥0.8
Cerebrospinal fluid [44]	≥0.0

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Guideline

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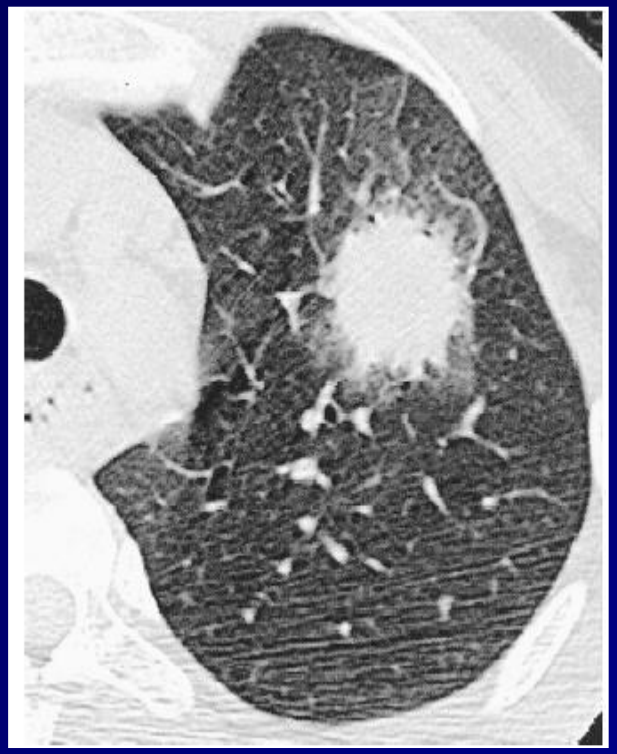
Drug-Drug Interactions to Watch Out for When Treating Invasive Aspergillosis

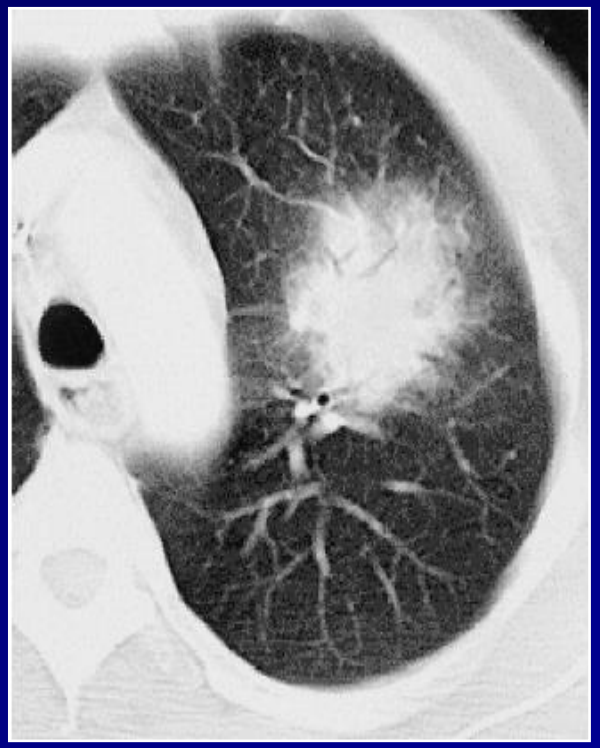
Coadministered Drug	Effect on Drug Levels	Effect on Antifungal	Potential Clinical Effects	DDI Severity Ranking	Management Strategies*
Posaconazole (strong CYP3A4 inhibitor; P-gp inhibitor and substrate)					
Venetoclax	↑ Venetoclax (AUC: 90-144%)	No significant change	Hematologic toxicity, GI toxicity, tumor lysis syndrome	Major	CLL/SLL at steady state dose: reduce venetoclax to 70-100 mg/day; AML patients: 10 mg on day 1, 20 mg on day 2, 50 mg on day 3, then 70-100 mg/day starting on day 4
Ibrutinib	↑ Ibrutinib (3- to 10- fold increase in exposure)	No significant change	Hematologic toxicity, bleeding, infection	Major	If coadministered with posaconazole oral suspension 200 mg t.i.d. or 400 mg b.i.d. or posaconazole delayed release tablets or i.v. once daily, reduce ibrutinib to or 140 mg/day p.o. for chronic GVHD.
Ruxolitinib	↑ Ruxolitinib	No significant change	Thrombocytopenia, anemia, elevated liver enzymes, diarrhea	Major	No initial dose adjustments necessary for patients with GVHD.
Bortezomib	↑ Bortezomib	No significant change	Myelosuppression, peripheral neuropathy, GI toxicity	Moderate	Use with caution; monitor bortezomib toxicity.
Idelalisib	↑ Idelalisib (AUC: 1.8-fold)	No significant change	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	No recommendation for dose adjustment.
Duvelisib	↑ Duvelisib (AUC: 2-fold)	No significant change	Myelosuppression, infection, elevated liver enzymes, enterocolitis	Major	Reduce duvelisib dose to 15 mg p.o. b.i.d.
Tacrolimus	↑ Tacrolimus (C_{max} 2-fold; AUC: 4.5-fold)	No significant change	Nephrotoxicity, neurotoxicity, hyperkalemia, electrolyte abnormalities	Major	Dosage reduction of tacrolimus is recommended.
Sirolimus	↑ Sirolimus (C_{max}: 572%; AUC: 788%)	No significant change	Hypertension, peripheral edema, hepatotoxicity, impaired wound healing, ILD	Severe	Dosage reduction of sirolimus is recommended.
Cyclosporine	↑ Cyclosporine	No significant change	Nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension	Major	Dosage reduction of cyclosporine is recommended.
Voriconazole (strong CYP3A4 and CYP2C9 inhibitor; CYP2C19 inhibitor; CYP2C19, CYP2C9, and CYP3A4 substrate)					

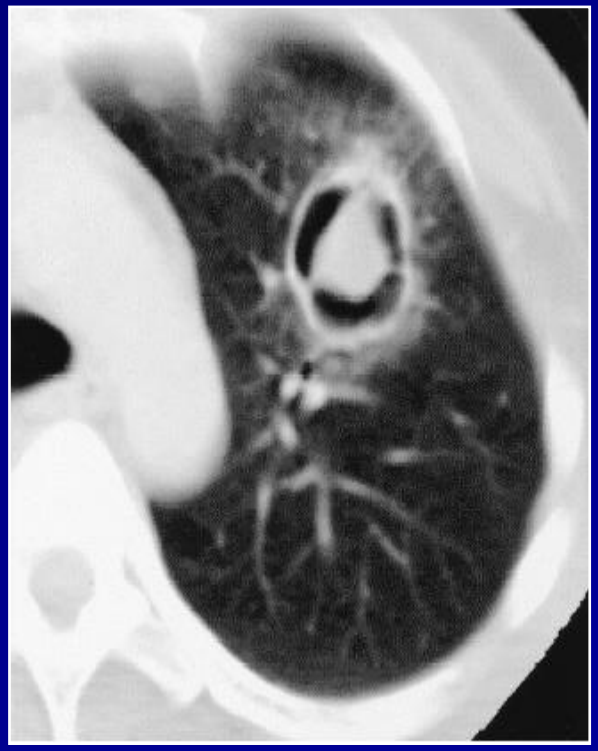
BT'de Bulguların Seyri

Caillot et al. J Clin Oncol 2001,19:253.

Erken BT
Seri BT







Gün 0
Halo

Gün 4
İnfilt
Halo

Gün 10
Hava-hilal

Ampirik ya da Pre-emptif Antifungal Tedavi

- Pre-emptif antifungal tedavi

- Olası invaziv mantar infeksiyonu göstergelerinden herhangi biri pozitif saptanırsa, antifungal tedaviye başlanmalıdır

- Düşük riskli hastalarda, invazif mantar infeksiyonu riski düşüktür, ampirik antifungal tedavi önerilmemektedir **(A-III)**

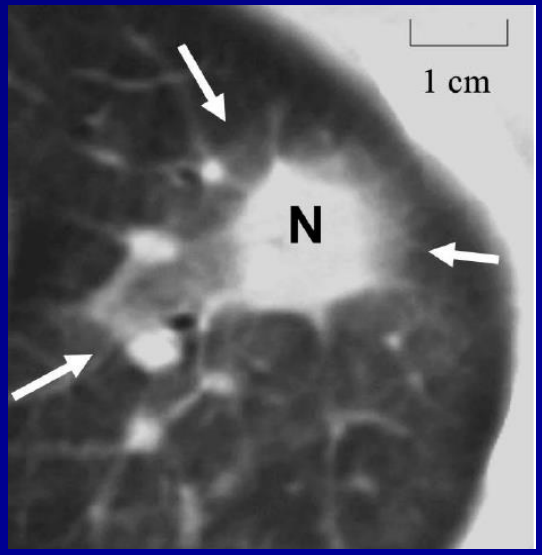
Kanıtlanmış İFİ tedavisi

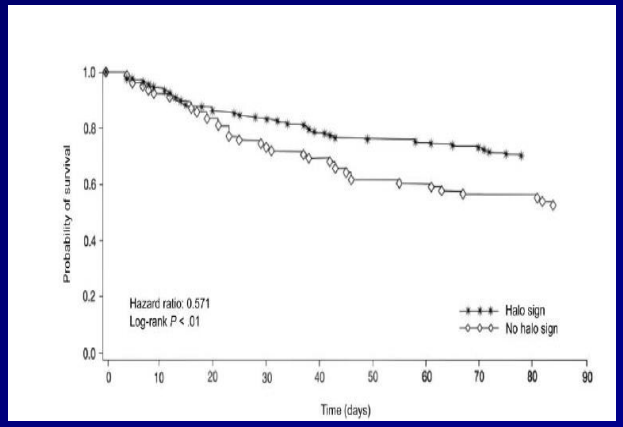
MAJOR ARTICLE

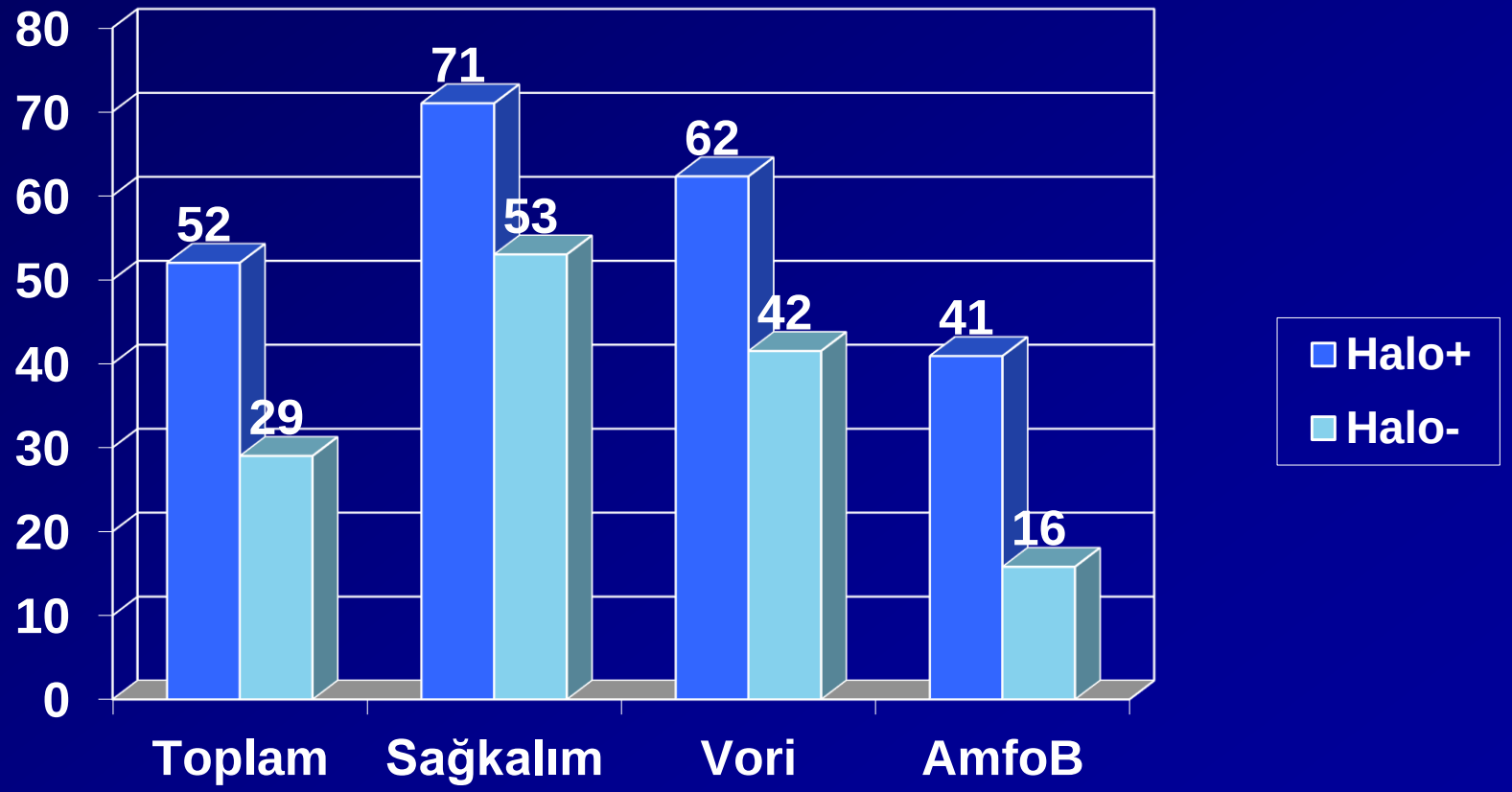
Imaging Findings in Acute Invasive Pulmonary Aspergillosis: Clinical Significance of the Halo Sign

Reginald E. Greene,[1] Haran T. Schlamm,[3] Jörg-W. Oestmann,[8] Paul Stark,[4] Christine Durand,[9] Olivier Lortholary,[10] John R. Wingard,[5] Raoul Herbrecht,[12] Patricia Ribaud,[11] Thomas F. Patterson,[6] Peter F. Troke,[13] David W. Denning,[14] John E. Bennett,[7] Ben E. de Pauw,[15] and Robert H. Rubin[2]

- 235 İPA sistematik değerlendirme
- Tedavi yanıtları
- 12. hafta sağ kalım oranları
- 143 halo
- 79 diğer radyolojik bulgular
- %94 makronodül
  - %61 halo




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


80
70
60
50
40
30
20
10
0
52
29
71
53
62
42
41
16
Toplam
Sağkalım
Vori
AmfoB
Halo+
Halo-

Clinical Microbiology and Infection xxx (2018) e1–e38

Contents lists available at ScienceDirect

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Pulmoner aspergilloz'da hedefe yönelik tedavi

- İsavukonazol 200mg IV **(A-I)**
  1. ve 2.gün 3x1, 200mg 1x1 idame
- Vorikonazol **(A-I)**
  1. gün--6mg/kg 2x1 iv (oral 400mg 2x1),
  idame--2x4 mg/kg iv (oral 200-300mg 2x1)
- L-AmB 3mg/kg **(B-II)**
- Vorikonazol + anidulafungin **(C-I)**
- Kaspofungin 70mg yükleme, 50mg idame **(C-II)**

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ELSEVIER

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American Society of Transplantation and Cellular Therapy Series. 2: Management and Prevention of Aspergillosis in Hematopoiet Transplantation Recipients

Sanjeet S. Dadwal[1,*], Tobias M. Hohl[2], Cynthia E. Fisher[3], Michael Boeckh[4], Ge Paul A. Carpenter[5], Brian T. Fisher[6], Monica A. Slavin[7], D.P. Kontoyiannis[8]

Article history:
Received 6 October 2020
Accepted 7 October 2020

- İPA şüphesinde BAL yapılmalı
- Radyolojik bulgular düzelene kadar en az 12 hafta tedavi edilmeli.
- Radyolojik değerlendirme en erken 2 hafta sonra yapılmalı
- GM izlemi klinik yanıtı değerlendirmede önemli ancak tek başına tedaviyi kesmek için yetersiz.
- SSS İA da vorikonazol veya isavukonazol
- GVHD tedavisi süresince AF tedavi devam etmeli
- Vorikonazol ilaç düzeyi 5-7 günde bakılmalı 2- 5.5 mcg/ml.
- Posakonazol ilaç düzeyi 3-8 günde >0.8 mcg/ml (prophylaksi)
- İsavukonazol TDM net değil

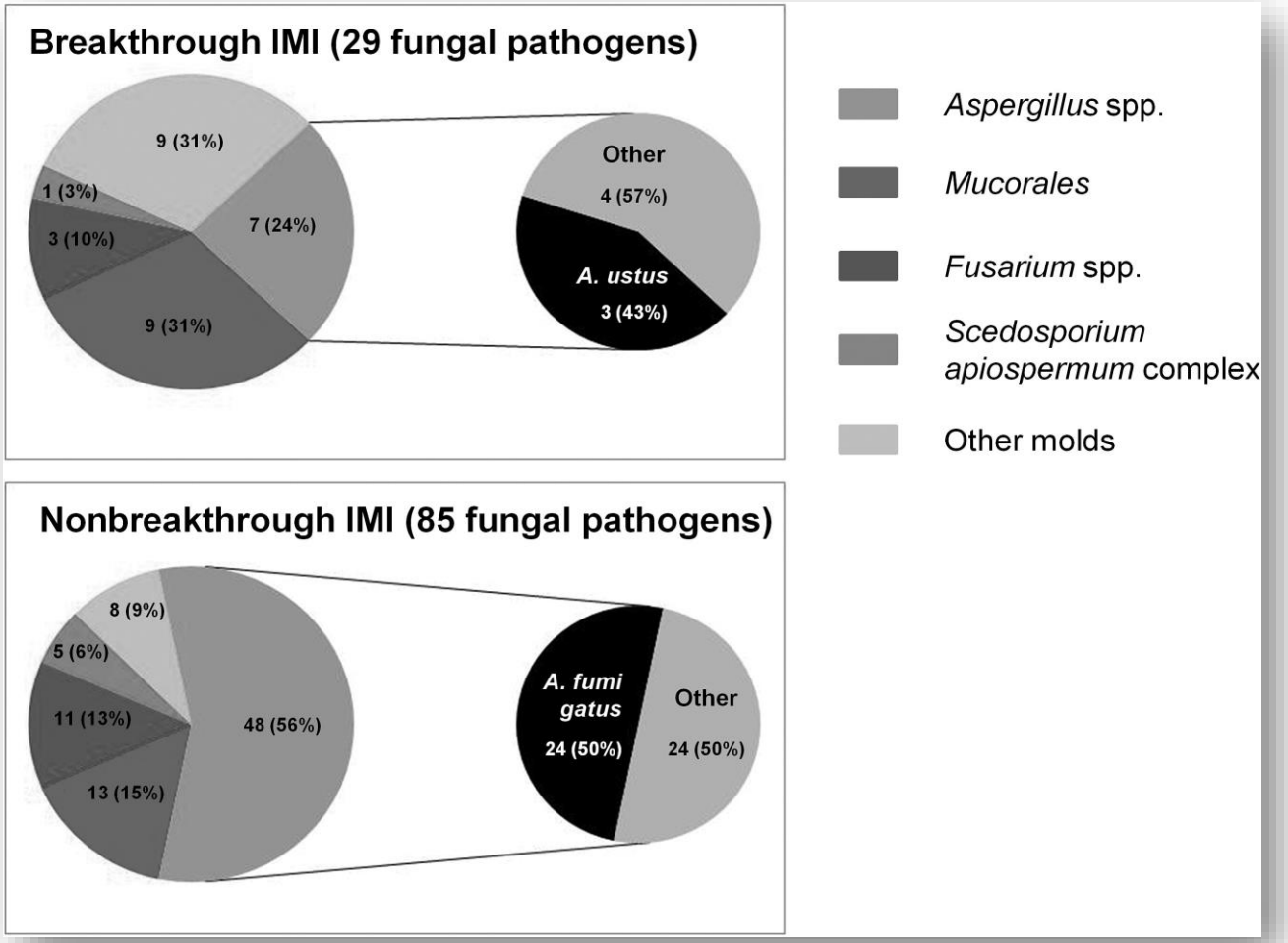
Sekonder profilaksi

- Geçirilmiş invaziv aspergilloz öyküsü olup;
  - Allojenik kök hücre nakili yapılacak
  - 7 günden uzun < 500/µL olacak şekilde nötropeniye girmesi beklenen hastalar
  - Akut GVHD
  - Yoğun, kronik GVHD
  - T hücre süpresyonu yapan tedaviler

- Daha önce etkin olduğu kanıtlanmış, aspergillus aktif bir ajan seçilmeli **(A-II)**
- Vorikonazol **(A-II)**
- Kaspofungin 70mg yükleme, 50mg idame engrafman olana kadar, idame olarak itrakonazol 400mg süsp **(B-II)**
- L-AmB sonrası, vorikonazol **(C-II)**

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

Azol profilaksisi ile değişen epidemiyoloji



Lamoth F. CID 2017

Breakthrough enfeksiyonda Aspergillus dışı mantarlar daha fazla (%76 vs %44; P = .003)

- Seyrek küfler
  - Mucorales,
  - Fusarium spp.,
  - Scedosporium apiospermum complex

Lamoth F. CID 2017

Diğer küfler

- Mukormikoz bazı merkezlerde 2. sırada etken
  - Sinüzit, DM, kortikosteroid kullanımı

- Aspergilloz dışı küf enfeksiyonları KİT sonrası geç dönemde ve uzun süreli antifungal kullanımı sonrasında görülür
  - Mortalite %70-80

Colombo AL. *Lancet Infect Dis* 2017

CORRECTED PROOF

Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study

Pieter P Lestrade ✉, Robbert G Bentvelsen, Alexander F A D Schauwvlieghe, Steven Schalekamp, Walter J F M van der Velden, Ed J Kuiper, Judith van Paassen, Ben van der Hoven, Henrich A van der Lee, Willem J G Melchers, ... Show more

Clinical Infectious Diseases, ciy859, https://doi.org/10.1093/cid/ciy859
Published: 11 October 2018 **Article history** ▾

- 2011-2015 retrospektif kohort
- 196 hasta
- Azol dirençli & duyarlı *A. fumigatus*
- 42. ve 90. gün mortalite
- Azol dirençli 37 hasta (%19), duyarlı 159(%81)

CORRECTED PROOF

Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study

Pieter P Lestrade ✉, Robbert G Bentvelsen, Alexander F A D Schauwvlieghe, Steven Schalekamp, Walter J F M van der Velden, Ed J Kuiper, Judith van Paassen, Ben van der Hoven, Henrich A van der Lee, Willem J G Melchers, ... Show more

Clinical Infectious Diseases, ciy859, https://doi.org/10.1093/cid/ciy859
Published: 11 October 2018 **Article history** ▾

Azol dirençli grupta artmış mortalite

- 49% vs 28%; P = .017 (42. gün)
- 62% vs 37%; *P* = .0038 (90. gün)

Azol direnci için test endikasyonları

- Azol direnci olduğu bilinen hastalarda veya bölgelerde, klinik kültürlerde aspergillus üretilmesi halinde **(A-II)**

- Azol direnci açısından yüksek prevalansı olan gruplar ve tedaviye yanıtsız hastalarda **(A-III)**

- *A.fumigatus* izolatları **(B-III)**

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

İntrensek dirençte antifungal rejimler

- Amfoterisin B MIC ≥ 1 mg/L ⟶ Azol duyarlıysa azole geç **(B-II)**

- *A.terreus* ise amfoterisin B doğal dirençli;

  Vorikonazol, isavukonazol **(A-II)**

  Posakonazol, itrakonazol **(B-III)**

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

Azol direncinde tedavi

- Vorikonazol MIC = 2 mg/mL ⟶ Vorikonazol + ekinokandin
  L-AmB **(A-III)**

- Vorikonazol MIC > 2 mg/mL
  L-AmB **(A-II)**
  Vorikonazol + anidulafungin **(B-III)**
  AmB lipid kompleks **(C-III)**
  Posakonazol + kaspofungin **(C-III)**
  Kaspofungin / mikafungin **(C-III)**

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

Refrakter hastalıkta tedavi

- Başka gruptan bir ilaca geçmek **(A-III)**
- Kombinasyon tedavisi **(C-III)**

- Vorikonazol **(A-II)**
- L-AmB 3 – 5 mg/kg **(B-II)**
- ABLC 5 mg/kg **(C-II)**
- Kaspofungin 70/50 mg 1x1 **(B-II)**
- Mikafungin 75 – 200 mg 1x1 **(C-II)**
- Posakonazol 200 mg 4x1 ya da 400mg 2x1 süsp / 300mg 2x1 1.gün, 1x1 idame **(B-II)**

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

ECIL-6 kılavuzu, Kandidemi

Kandidemi'de ilk seçenek tedavi önerileri[1]

	ECIL-6[1]	
	Genel popülasyon	Hematolojik hastalar
Liposomal amfo B	**AI**	**AII**
Kaspofungin	**AI**	**AII**
Vorikonazol*	**AI**	**BII**
Flukonazol*,†	**AI**	**CIII**
Anidulafungin	**AI**	**AII**
Mikafungin	**AI**	**AII**

* Çok şiddetli stabil olmayan hastalarda önerilmemektedir.

† Daha önceden azol kullanmış olanlarda önerilmemektedir.

A: İyi kanıt, **B:** Orta kanıt, **C:** Zayıf Kanıt,

I: Birden fazla düzgün randomize kontrollü çalışma,
II: Randomizasyon olmadan kohort ya da olgu-kontrol analitik çalışmalarından iyi tasarlanmış birden fazla klinik çalışma,
III: Klinik deneyim, tanımlayıcı çalışmalar ya da uzman komite raporlarına dayalı saygıdeğer otoritelerin görüşlerinden kanıtlar.

Tablo, 1 numaralı referanstan uyarlanmıştır.

İFi: İnvazif Fungal İnfeksiyon

Referans:1. Tissot F et al. Haematologica 2017; 102(3):433-444.

Türe Göre Kandidemi Tedavi

Table 5. ECIL-6 recommendations for first-line treatment of candidemia after species identification.

Candida species	Overall population		Hematologic patients	
C. albicans	Echinocandins[a]	A I	Echinocandins	A II
	Fluconazole[b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins[a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins[a]	A II	Echinocandins[a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins[c]	B II	Echinocandins	B III

[a]Same grading for anidulafungin, caspofungin, micafungin; [b]not in severely ill patients; [c]if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72 h), continuing use of echinocandin might be considered.

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Antimicrobial Chemotherap

Introduction of an antifungal stewardship programme targeting high-cost antifungals at a tertiary hospital in Cambridge, England

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Background: Antifungal stewardship aims to promote the optimal use of antifungals through the careful selection of agents based on patient profile, target organism, toxicity, costs and the likelihood of emergence and spread of resistance.

Methods: We report on an observational prospective 12 month study conducted by an antifungal stewardship team targeting the use of echinocandins (caspofungin and micafungin), voriconazole and liposomal amphotericin B in a tertiary referral hospital in the UK.

Results: One-hundred-and-seventy-three patients were reviewed on 294 occasions. Clinical advice was given and implemented during review of 45 (88.2%) of micafungin prescriptions, 70 (78.7%) of those receiving voriconazole, 78 (62.4%) of those receiving liposomal amphotericin B and 3 (27.3%) of those receiving caspofungin. Except for voriconazole, nearly half of all treatments reviewed were stopped or changed. This study found that a crude cost saving of ~£180000 in antifungal drugs was generated compared with the previous year.

Conclusions: Using a multidisciplinary team, antifungal stewardship can achieve significant improvements in patient management and it may reduce costs.

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Antimicrobial Chemotherapy

Management bundles for candidaemia: the impact of compliance on clinical outcomes

Yoshio Takesue[1,2]*, Takashi Ueda[2], Hiroshige Mikamo[1], Shigeto Oda[1], Shunji Takakura[1], Yuko Kitagawa[1] and Shigeru Kohno[1] on behalf of the ACTIONs Project†

Table 2. Bundle elements in patients with candidemia.

Phase	Elements	Adjusted OR (95% CI) Impact of individual bundle elements	
		Clinical success	*Mortality*
Bundles to be accomplished at the start of therapy	Removal of existing CVCs within 24 h of diagnosis	2.97 (1.51–5.85)	0.41 (0.23–0.74)
	Appropriate initial selection of antifungals	–	–
	Appropriate dosing of antifungals	–	–

Tedavi başlangıcında gerçekleştirilecek paket

- **SVK tanıdan sonra ilk 24 saatte çıkar**
- **Uygun antifungal**
- **Uygun dozda antifungal**

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Klinik başarı

Uyum olan vs olmayan

% 92,9 vs % 75,8 (p=0,011)

Table 4. Impact of compliance with the bundles on clinical outcomes in patients with candidaemia

	Clinical success				Mortality			
Definition of compliance	patients with compliance no. of patients (%)	patients without compliance no. of patients (%)	crude OR (95% CI)	adjusted OR (95% CI)	patients with compliance no. of patients (%)	patients without compliance no. of patients (%)	crude OR (95% CI)	adjusted OR (95% CI)
Achievement of all evaluable bundle elements	39/42 (92.9)	429/566 (75.8)	4.15 (1.26–13.7)	3.93 (0.90–17.17)	2/24 (8.3)	125/455 (27.5)	0.24 (0.06–1.04)	0.15 (0.07–1.50)
Achievement of all evaluable bundle elements except oral switch	121/130 (93.1)	347/478 (72.6)	5.08 (2.50–10.29)	4.42 (2.05–9.52)	10/97 (10.3)	117/383 (30.5)	0.26 (0.13–0.52)	0.27 (0.13–0.57)

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Antimicrobial Chemotherapy

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28. Gün mortalite

Uyum var vs yok

% 10.3 vs % 30.5

Table 4. Impact of compliance with the bundles on clinical outcomes in patients with candidaemia

	Clinical success				Mortality			
Definition of compliance	patients with compliance no. of patients (%)	patients without compliance no. of patients (%)	crude OR (95% CI)	adjusted OR (95% CI)	patients with compliance no. of patients (%)	patients without compliance no. of patients (%)	crude OR (95% CI)	adjusted OR (95% CI)
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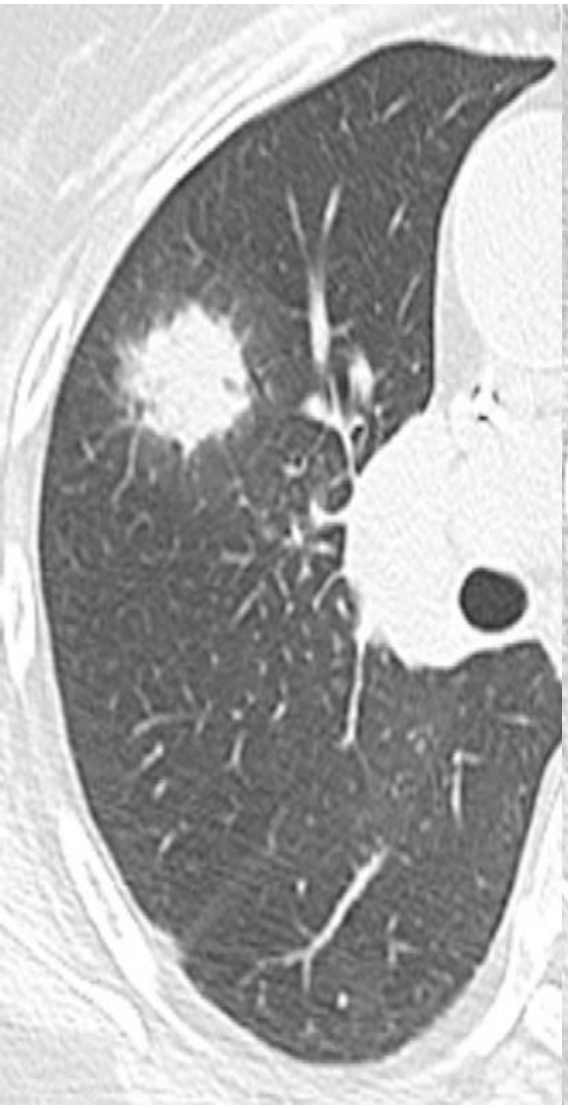
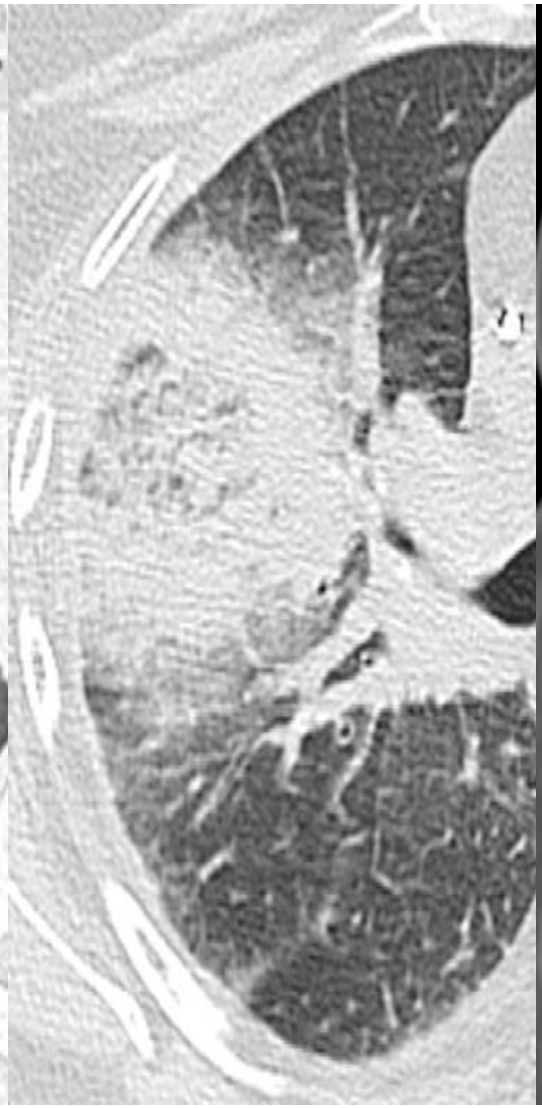
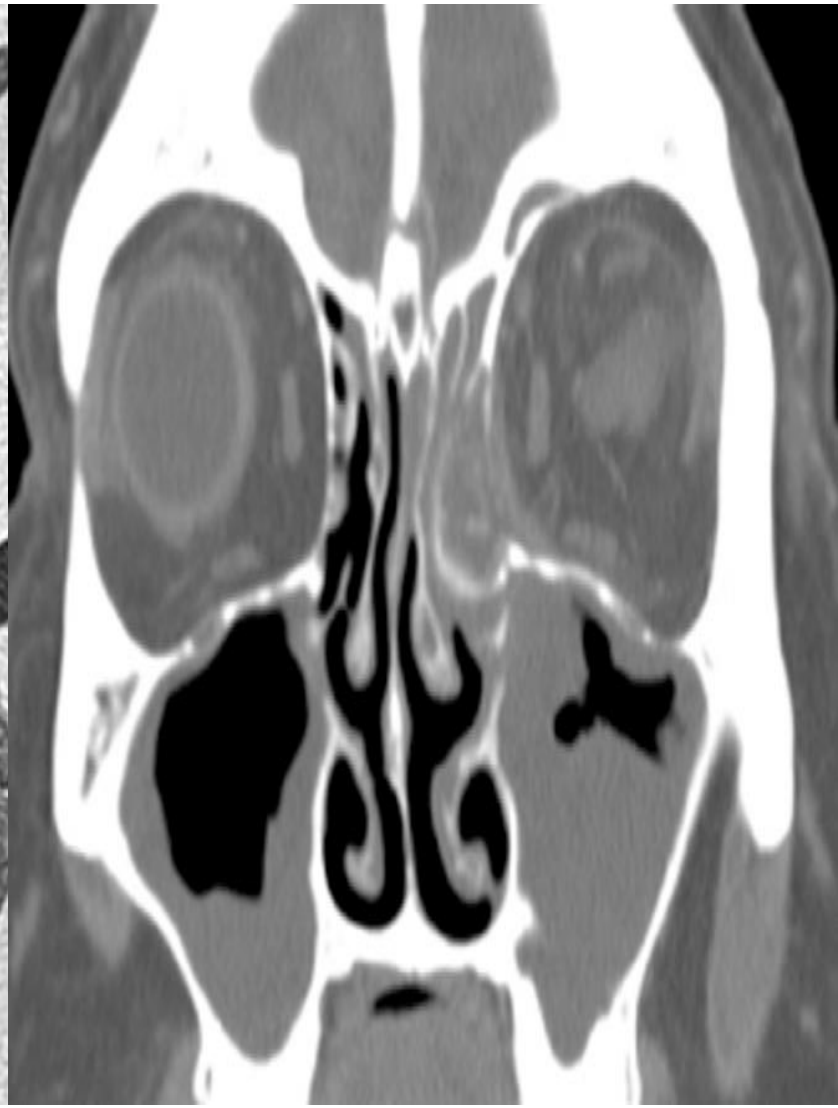
Zigomikoz
Ne zaman düşünülmeli

- Paranazal sinüs tutulumu
- Yumuşak damakta nekroz
- Vorikonazol profilaksisi altında gelişen fungal enfeksiyon
- Histopatolojik incelemelerde septasız hif
- Akciğer BT 10’ dan fazla nodül, plevral effüzyon
- Diyabet
- Radyolojik ve klinik bulgular (+), galaktomannan ve 1,3 beta D glukan(-)

Radyoloji







The Reversed Halo Sign: Pathognomonic Pattern of Pulmonary Mucormycosis in Leukemic Patients With Neutropenia?

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CID 2014:58

752 hasta

16Mukor

Radyolojik bulgular	
>3 cm kitle	%88
En büyük lezyonun çapı	4,55 (1,7-9,9) cm
Solit lezyon	%94
Ters halo	**%94 (erken bulgu)**
Hava hilal	%0
Plevral effüzyon	%12
Tanı	
BT eşliğinde biyopsi	%50
Cerrahi akciğer rezeksiyon	%31

Tedavi yaklaşımı
Erken cerrahi + Antiungal

Antifungal kemoterapi	Doz	Kanıt
Amfoterisn B Deoksikolat		C2
Liposomal Amfo B	5-10 mg/kg	B2
Amfoterisin B lipit kompleks	5-7,5 mg/kg	B2
Amfoterisin B kolloidal dispersiyon		C2
Posaconazol	2x400mg	C3
Kombinasyon		C3

Tedavi yaklaşımı

- Antifungal kemoterapi — B2
  - Liposomal Amfo B
  - Amfoterisin B lipit kompleks
- Altta yatan hastalığın kontrolü — A2

  (DM, Nötropeni, Steroit, Deferroxamin)
- Cerrahi — A2
  - Rinoserebral, deri ve yumuşak doku enfeksiyonu

A2

Özet

- FEN hastada İFİ mortalitede önemini koruyor
- Rehberlere uyum değerlendirilmeli
- Gerçek yaşam verileri

Teşekkür ederim