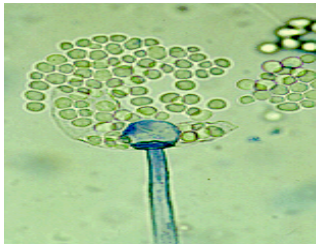
İSTANBUL
MEDENİYET ÜNİVERSİTESİ

MUKORMİKOZ

Yrd. Doç. Dr. Yasemin Çağ

İstanbul Medeniyet Üniversitesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD



- En sık üçüncü IFI
  - (kandidiyazis ve aspergillozis'den sonra)

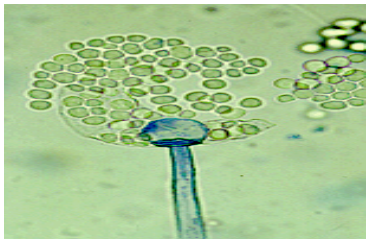
- 0.12-0.17 /100.000 popülasyon
- Sıklığı giderek artmakta !

  - Bitar D *et al*. *Emerg Infect Dis* 2009
  - Rees JR et al. *Clin Infect Dis* 1998

- Uygun tedaviye rağmen yüksek mortalite (24% - 49%)

  - Skiada A *et al*. *CMI* 2011
  - Rüping MJ *et al*. *JAC* 2010

Mucorales Takımı



- *Rhizopus (*En yaygın *)*
  - *Rhizopus oryzae*
- *Lichtheimia* (öncesinde *Absidia*)
- *Mucor*
- *Cunninghamella* (Yüksek mortalite, virulans)
  - Gomes MZ et al. *Clin Microbiol Rev* 2011
  - Petraitis V et al. *Med Mycol* 2013
- *Rhizomucor*, *Apophysomyces*, *Saksenaea*

Epidemiyoloji ve Patogenez

- Çürümüş organik materyal ve toprak
- Agustos ve Eylül aylarında daha sık
- Konidiaların solunması, hasarlı deri veya mukozadan direk inokülasyon, gastrointestinal sistem
- Damar invazyonu, trombüs, nekroz, infarkt
- Kan, komşuluk ve sinirler yoluyla yayılım

Risk Faktörleri

- Hematolojik malignite (AML) / HSCT
- Uzamış/ciddi nötropeni
- Kontrolsüz diabet
- Solit organ malignitesi/transplatasyon
- Aşırı demir yüklenmesi, deferoxamin tedavisi
- Uzun süreli vorikonazol kullanımı

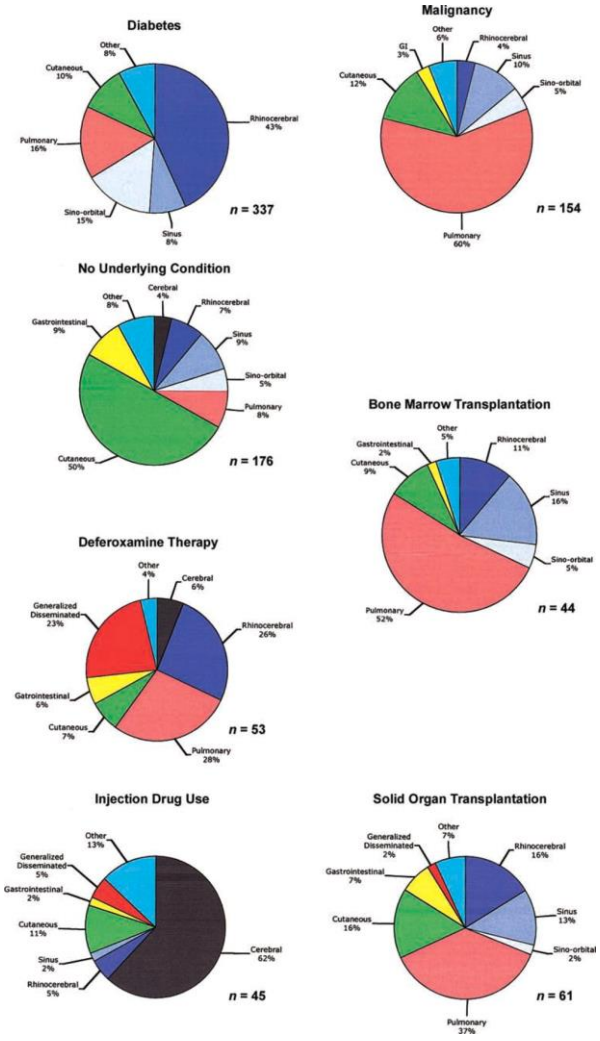
- Major travma
  - Yanık, penetran travma, cerrahi yara
- Uzamış kortikosteroid kullanımı
- Böbrek yetmezliği
- HIV
- İV ilaç alışkanlığı
- Malnutrisyon
- Prematurite

Petrikkos et al. CID 2012

Klinik Prezentasyon

- Rino-orbito-serebral
- Pulmoner
- Kutanöz
- Gastrointestinal
- Dissemine
- Diğer (Renal, hepatik, endokardit, peritonit)

Patterns of zygomycosis, by host population.



Maureen M. Roden et al. 2005

Clinical Infectious Diseases

Tanı

- Risk faktörleri + klinik veya radyolojik şüphe
- Kesin tanı için klinik örnek gerekli (Biyopsi, BAL, balgam, BOS)
- Direk mikr
- Kültür
- Histopatoloji

Trombositopeni !!!

Klinik Şüphe !!!

Risk faktörleri olan hastada

- İmmun supresif ve kontrolsuz diyabeti olan

- Yüzde veya sino-orbital bölgede hızlı ilerleyen enfeksiyon
- Nekrotik skar
- Eşlik eden ani gelişen diplopi varlığında

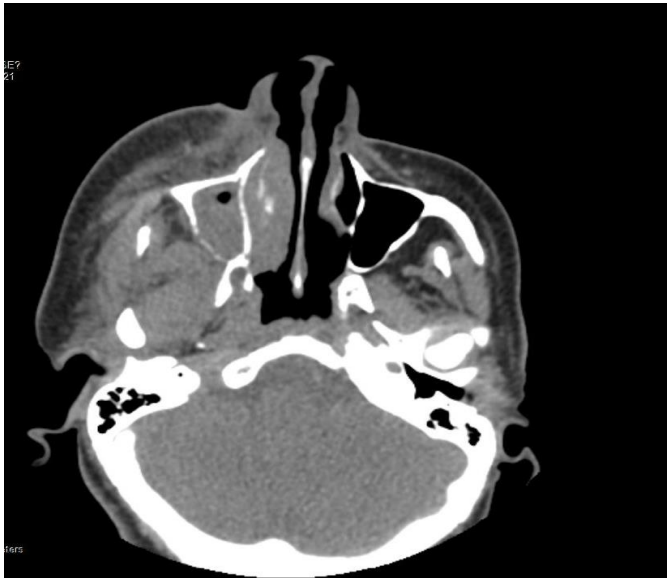
Rino-orbito-serebral tutulum düşünülmeli

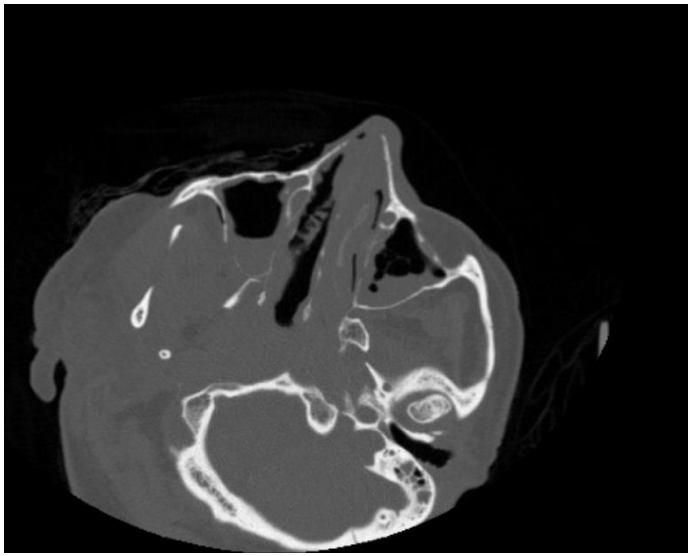
Görüntüleme

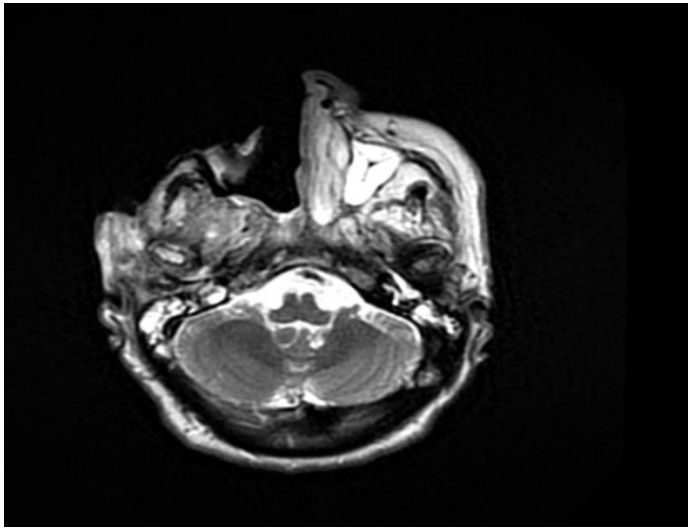
- Tanı ve takipte yol gösterici
  - CT (sinüs, AC)
  - MRI (orbita, cranium, GİS)

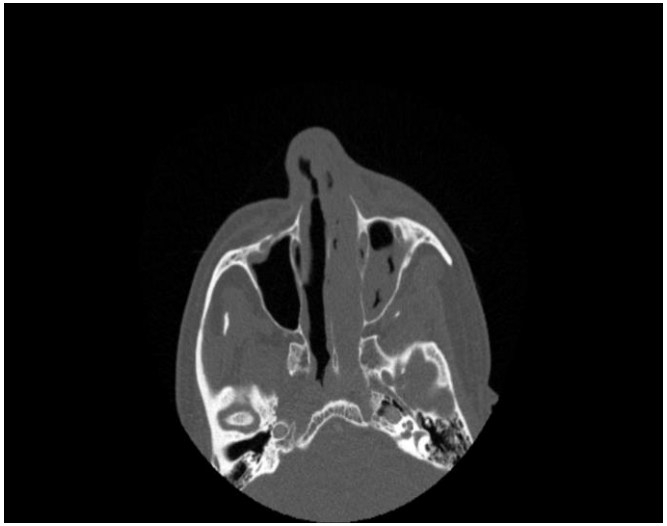
Görüntüleme

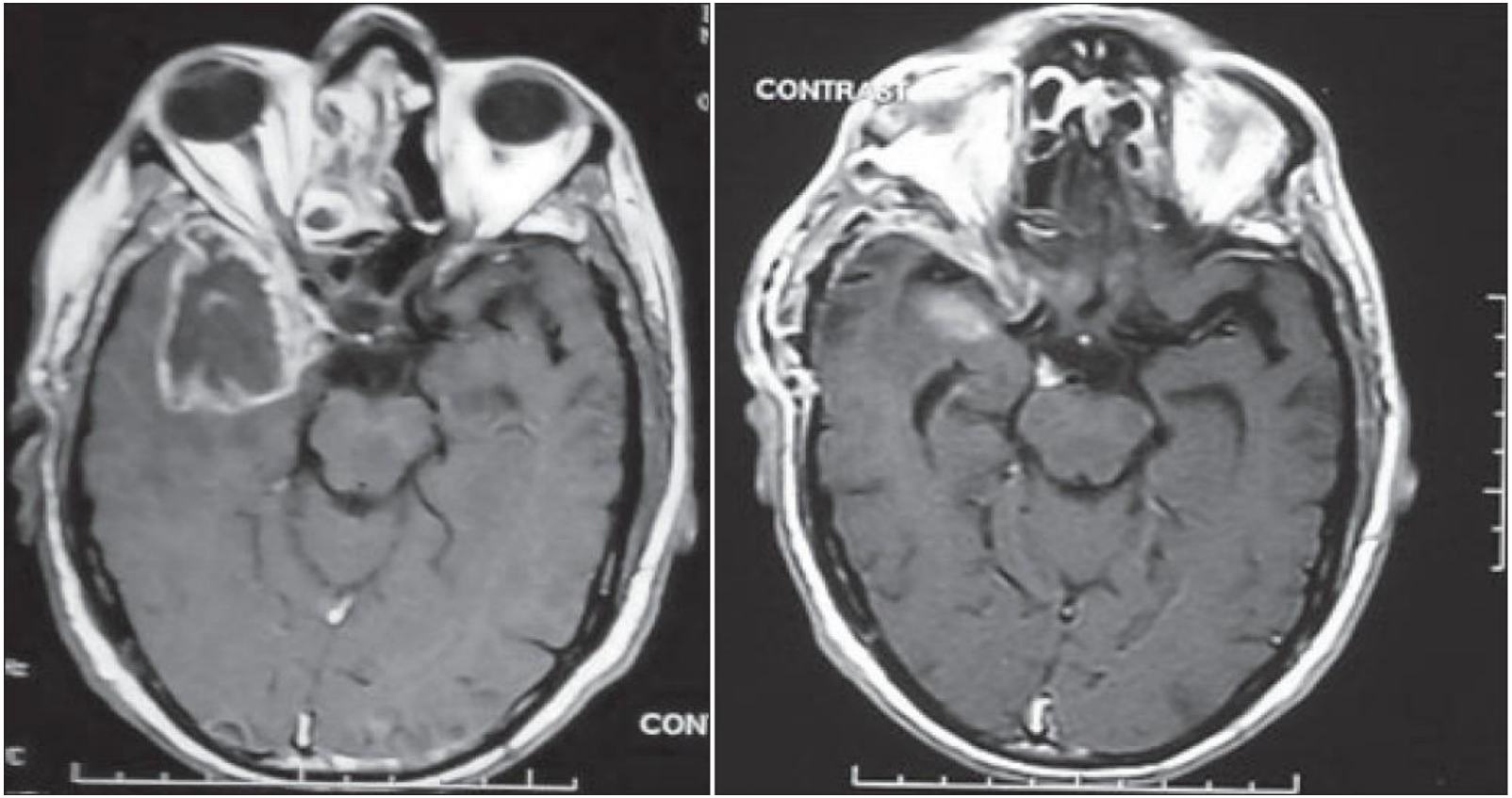
- Akciğer: Çoğunlukla aspergillus (Hematolojik maligniteli hastalarda mucor'un en sık tutulduğu alan)
  - Ters halo: Çoğunlukla mucor (Fakat, tuberküloz, aspergillus…..)
  - >10 nodüler infiltrat
  - >3 cm nodül
  - Plevral efüzyon
  - Halo: Çoğunlukla aspergillus (Mucor, tuberculosis, CMV, nocardia……)
- Rhino-orbita-cerebral : Hematolojik maligniteli hastada çoğunlukla mucor (Fakat, aspergillus….)
  - Kemik yıkımı
  - Mukozal kalınlaşma
  - İntrakranial yayılım

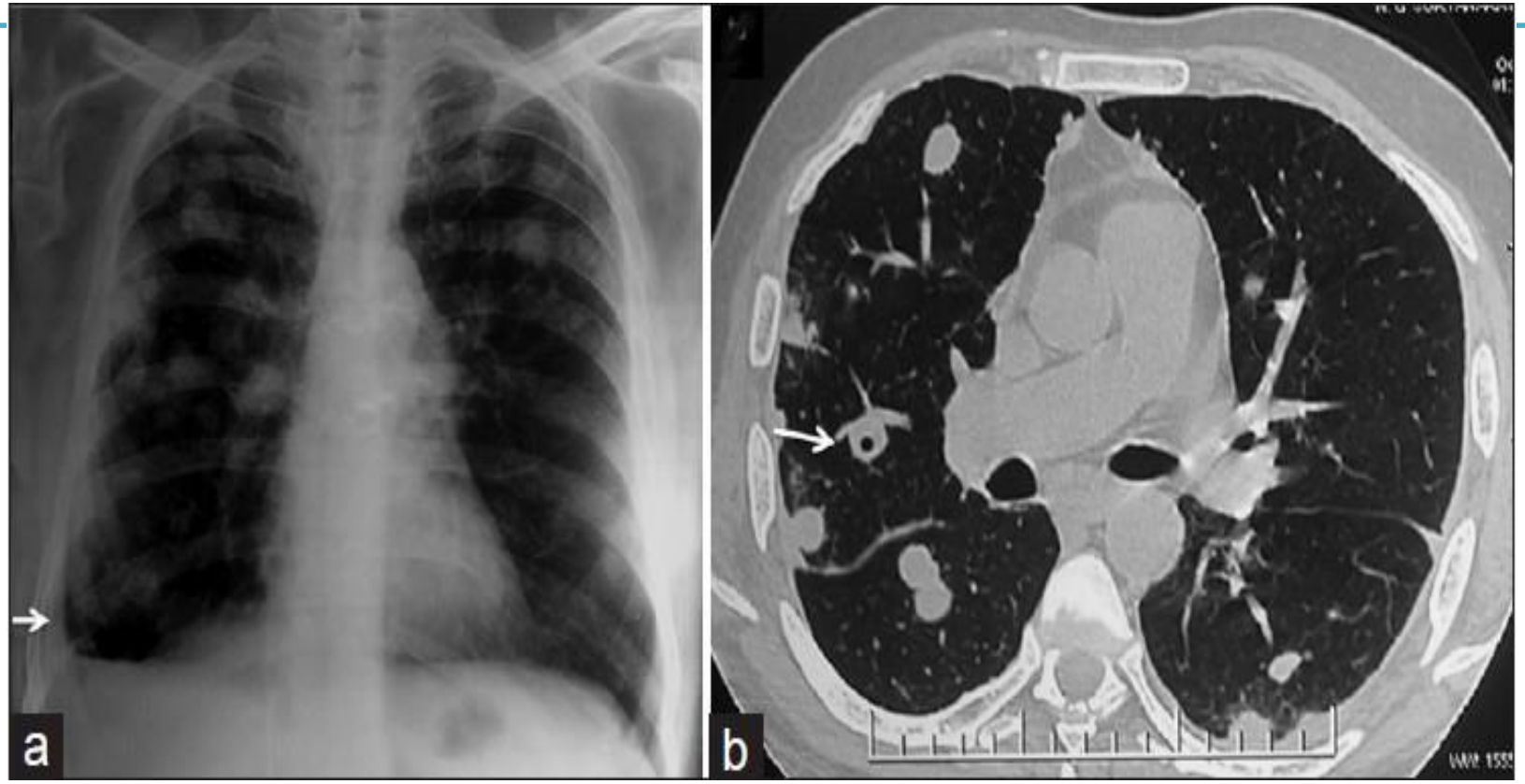


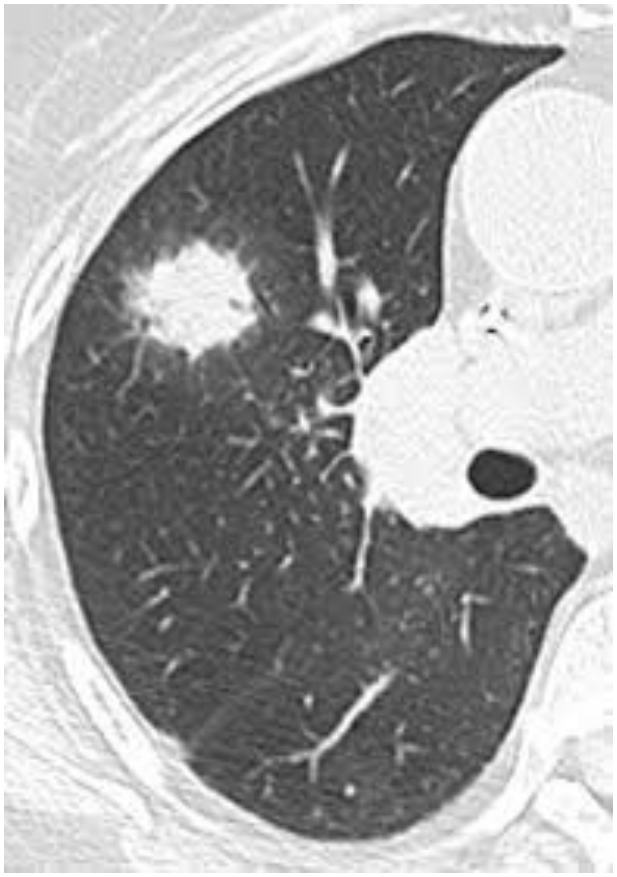


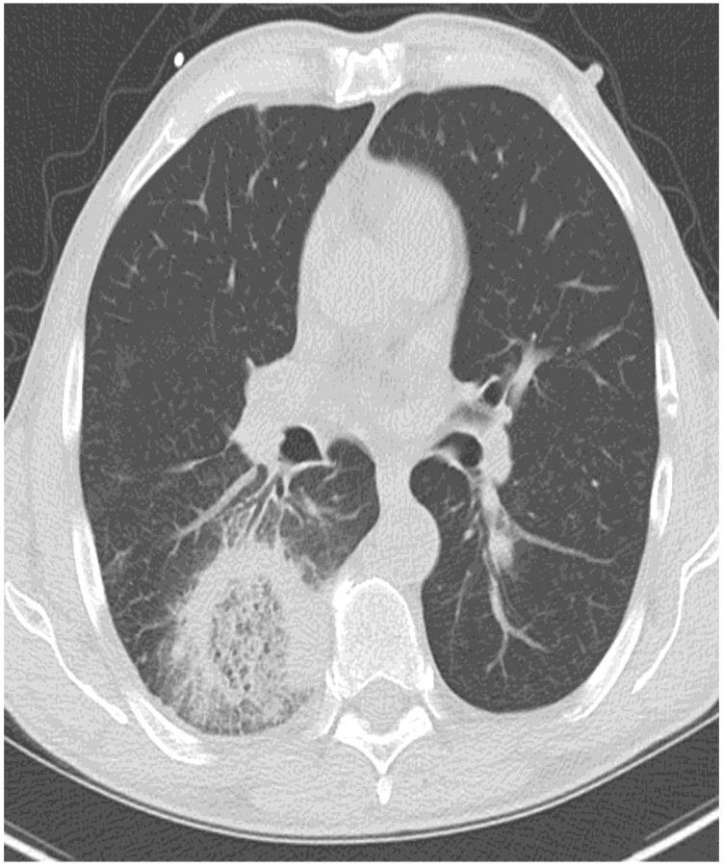





CON
CONTRAST

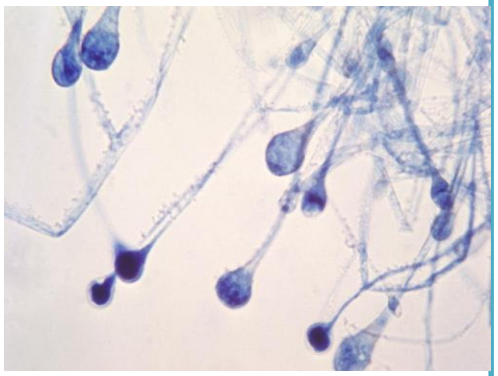

a
b





Mikrobiyolojik İnceleme

- Direk mikroskopi: Hızlı, yol gösterici, kültürle doğrulanmalı
- KOH ile muamele, kalkoflor beyazı veya Gomori methamine- silver ile boyama
  - Hiyalen
  - Septasız, veya seyrek septalı
  - Serit benzeri dik açı ile dallanan
  - Geniş (6-16 µm) çaplı
  - Düzensiz, hifler



Kültür

- 25-**37C** de, genellikle 24-48 saatte ürer
- Petri kutusunu dolduran yünümsü örgüde koloni (3-5 gün)
- Biyopsi m
- Kan kültü
- BOS nadi
- **Cins ve tür düzeyinde tanımlama imkanı**

Amfoterisin B üremeyi baskılayabilir

- Etkenin cins ve tür düzeyinde tamınlanması antifungal tedaviyi yönlendirecek etkisi gösterilememiş

Salas V et al. AAC 2012

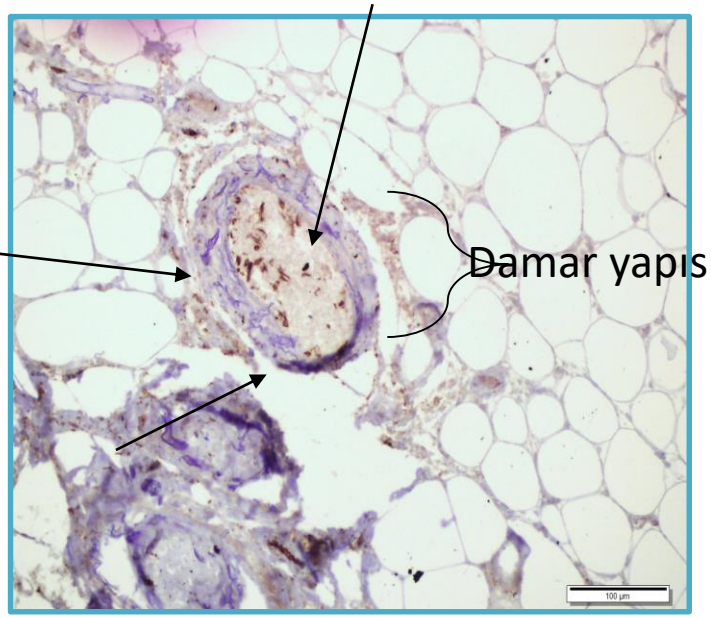
- Tür düzeyinde tanımlama epidemiyolojik veriler ve salgın araştırmalarında önemli

Rammaert B, et al. *CID* 2012

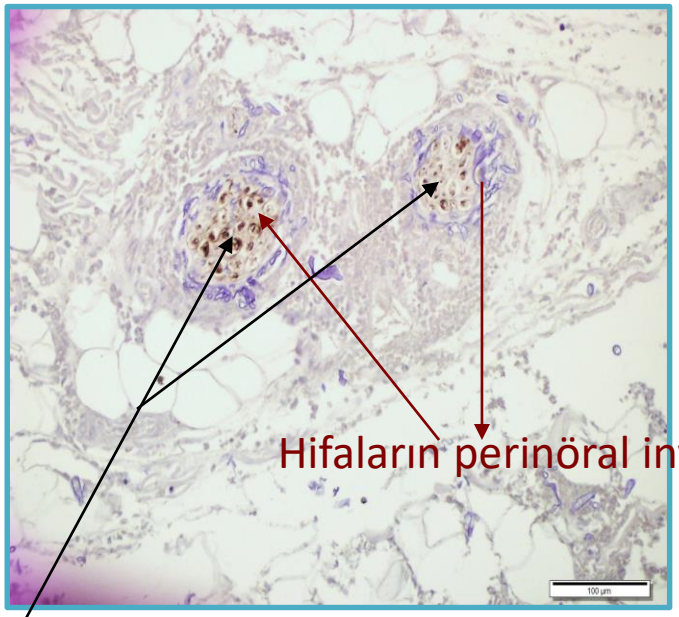
Histopatoloji

Tür ve cins ayırımı yapılamaz

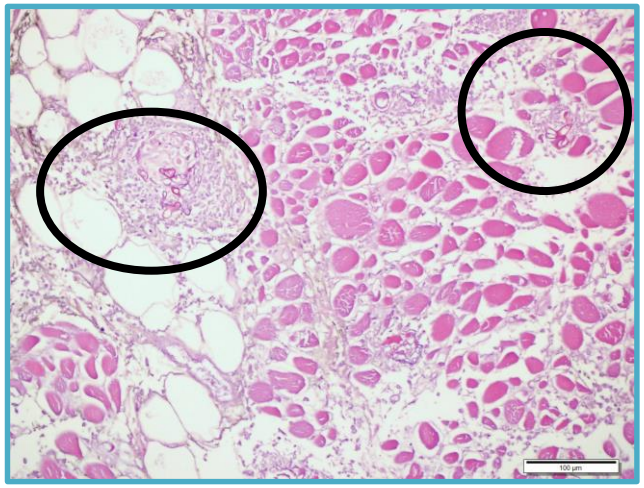
- **Nekrotik doku içinde Mucorales takımına ait fungal hifler**
- **Perinöral invazyon**
- İnfarkt (Hemorajik)
- Damar invazyonu
- Nötrofilik infiltratlar
- Granülom



Damar duvarlarında mantar hifaları



Sinir dokusu (s100 boyama)



Kas dokusu içerisinde geniş, ince duvarlı, irreguler Non-paralel konturlu tipik mucor hifaları

Serolojik Testler

- Galaktomannan: Negatif
- 1,3 Beta-D Glukan: Negatif

Yeni Tanısal Yaklaşımlar

- ELISPOT (Mucorales-specific T cells saptanması)
- Moleculer testler (PCR)
  - Taze klinik materyal
  - Parafi
  - Serum
  - Kültür
- MALDI-TOF

Henüz standardize edilememiştir

Tedavi

- Erken tanı
- Altta yatan hastalığın tedavisi
- Uygun ve erken cerrahi debritman
- Antifungal tedavi

Spellberg B. Clin Microbiol Rev 2005

Clin Infect Dis. 2008 Aug 15;47(4):503-9. doi: 10.1086/590004.

Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis.

Chamilos G[1], Lewis RE, Kontoyiannis DP.

Author information

Abstract

BACKGROUND: Zygomycosis is an emerging opportunistic mycosis among immunocompromised patients with a particularly poor prognosis.

METHODS: We analyzed the impact of delaying effective amphotericin B-based therapy on outcome among 70 consecutive patients with hematologic malignancy who had zygomycosis in our institution during the period 1989-2006. We used classification and regression tree analysis to identify the mortality breakpoint between early and delayed treatment.

RESULTS: Delayed amphotericin B-based therapy (i.e., initiating treatment >/=6 days after diagnosis) resulted in a 2-fold increase in mortality rate at 12 weeks after diagnosis, compared with early treatment (82.9% vs. 48.6%); this remained constant across the years of the study and was an independent predictor of poor outcome (odds ratio, 8.1; 95% confidence interval, 1.7-38.2; P = .008) in multivariate analysis. Active malignancy (P = .003) and monocytopenia (P = .01) at the time of diagnosis of infection were also independently associated with a poor out

CO

dia

her

Tedaviye erken başlanması mortaliteyi azaltır

PMID: 18611163 DOI: 10.1086/590004

Altta yatan koşulların kontrolü

- Diyabetin kontrolü
- Hasta nötropenikse hemopoietik growth faktör verilmesi
- Steroidin kesilmesi veya azaltılması
- Deferoxamin tedavisinin kesilmesi
- İmmun supresyonun azaltılması

Spellberg B. Clin Microbiol Rev 2005

Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases

Maureen M. Roden,[1] Theoklis E. Zaoutis,[2,3,4] Wendy L. Buchanan,[1] Tena A. Knudsen,[1] Tatyana A. Sarkisova,[1] Robert L. Schaufele,[1] Michael Sein,[1] Tin Sein,[1] Christine C. Chiou,[5] Jaclyn H. Chu,[2] Dimitrios P. Kontoyiannis,[5] and Thomas J. Walsh[1]

Treatment	No. (%) of all patients	No. of patients who survived/total no. who received the treatment (%)
Amphotericin B formulation		
Deoxycholate	532 (57)	324/532 (61)
Lipid	116 (12)	80/116 (69)
Itraconazole, ketoconazole, or posaconazole	15 (2)	10/15 (67)
No antifungal therapy	333 (36)	59/333 (18)
Surgery alone	90 (10)	51/90 (57)
Surgery and antifungal chemotherapy	470 (51)	328/470 (70)
Hyperbaric oxygen	44 (5)	28/44 (64)
Granulocyte colony-stimulating factor	18 (2)	15/18 (83)
Granulocyte transfusion	7 (1)	2/7 (29)
None	241 (26)	8/241 (3)

Maureen M. Roden et al. Clin Infect Dis. 2005;41:634-653

Clinical Infectious Diseases

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2002, p. 1581–1582 Vol. 46, No. 5
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.5.1581–1582.2002

In Vitro Activities of Posaconazole, Itraconazole, Voriconazole, Amphotericin B, and Fluconazole against 37 Clinical Isolates of Zygomycetes

Qiu N. Sun,[1,2] Annette W. Fothergill,[3]* Dora I. McCarthy,[3] Michael G. Rinaldi,[3,4] and John R. Graybill[1,4]

- **37 strains / 7 species of zygomycetes**
- **NCCLS M38-P; 48h; 80% inhibition (azoles) / 100% (Amb)**

	MIC_{50} [µg/mL]	MIC_{90} [µg/mL]
POS	0.25	4
ITC	0.5	8
VRC	>64	>64
FLC	>64	>64
AMB	0.25	0.5

İnvitro çalışmalarda amfoterisin B ve posakonazol mucorales takımına en etkili ajanlar

Amfoterisin B

- Amfoterisin-B Deoksikolat 1-1.5 mg/kg/gün
- Lipozomal Amfoterisin-B(LAB) 5-10 mg/kg/gün
- ABLC 5 mg/kg/gün

J Antimicrob Chemother 2015; **70**: 3116–3123
doi:10.1093/jac/dkv236 Advance Access publication 27 August 2015

Journal of Antimicrobial Chemotherapy

Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis

F. Lanternier[1,2], S. Poiree[3], C. Elie[4], D. Garcia-Hermoso[5,6], P. Bakouboula[4], K. Sitbon[5,6], R. Herbrecht[7], M. Wolff[8], P. Ribaud[9] and O. Lortholary[1,2,5,6]* on behalf of the French Mycosis Study Group†

Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis

*Francisco M Marty, Luis Ostrosky-Zeichner, Oliver A Cornely, Kathleen M Mullane, John R Perfect, George R Thompson III, George J Alangaden, Janice M Brown, David N Fredricks, Werner J Heinz, Raoul Herbrecht, Nikolai Klimko, Galina Klyasova, Johan A Maertens, Sameer R Melinkeri, Ilana Oren, Peter G Pappas, Zdeněk Ráčil, Galia Rahav, Rodrigo Santos, Stefan Schwartz, J Janne Vehreschild, Jo-Anne H Young, Ploenchan Chetchotisakd, Sutep Jaruratanasirikul, Souha S Kanj, Marc Engelhardt, Achim Kaufhold, Masanori Ito, Misun Lee, Carolyn Sasse, Rochelle M Maher, Bernhardt Zeiher, Maria J G T Vehreschild, for the VITAL and FungiScope Mucormycosis Investigators**

Lancet Infect Dis 2016

Published Online
March 8, 2016
http://dx.doi.org/10.1016/S1473-3099(16)00071-2

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(16)00127-4

Summary

Background Mucormycosis is an uncommon invasive fungal disease with high mortality and few treatment options. Isavuconazole is a triazole active in vitro and in animal models against moulds of the order Mucorales. We assessed the efficacy and safety of isavuconazole for treatment of mucormycosis and compared its efficacy with amphotericin B in a matched case-control analysis.

Methods In a single-arm open-label trial (VITAL study), adult patients (≥18 years) with invasive fungal disease caused by rare fungi, including mucormycosis, were recruited from 34 centres worldwide. Patients were given isavuconazole

Isavukonazol

- İkinci kuşak triazol
- Oral ve IV formları mevcut
- Mart 2015 mukormikoz için FDA onayı

Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis

Francisco M Marty, Luis Ostrosky-Zeichner, Oliver A Cornely, Kathleen M Mullane, John R Perfect, George R Thompson III, George J Alangaden, Janice M Brown, David N Fredricks, Werner J Heinz, Raoul Herbrecht, Nikolai Klimko, Galina Klyasova, Johan A Maertens, Sameer R Melinkeri,

	Isavuconazole	Amphotericin B	p value
Crude all-cause mortality, n/N (%; 95% CI)*	7/21 (33%; 14·6–57·0)	13/33 (39%; 22·9–57·9)	p=0·775†
Weighted all-cause mortality (%;‡ 95% CI)*	33%; 13·2–53·5	41%; 20·2–62·3	p=0·595§
Crude mortality by matching covariates, n/N (%)			
Haematological malignancy	5/11 (45%)	7/18 (39%)	NA
Severe disease¶	6/12 (50%)	8/13 (62%)	NA
Surgical treatment‖	4/9 (44%)	3/13 (23%)	NA

Primary treatment with isavuconazole-treated cases (VITAL) versus amphotericin B-treated controls (FungiScope). *95% CI are based on an exact binomial distribution (crude) or normal approximation (weighted). †Calculated from Fisher's exact test. ‡Weights were applied according to the ratio of the number of controls matched to each case. §Calculated from a χ^2 test. ¶CNS involvement or disseminated disease (defined as disease involving >1 non-contiguous organ). ‖Resection or debridement at the site of infection at treatment start (SD 7 days).

Table 5: All-cause mortality through day 42 for a matched case-control analysis of patients with mucormycosis

İsavukonazol ve AmB etkinlik açısından benzer bulunmuş

L-AmB ve posakonazol kombinasyon tedavisi

Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematologic diseases: a report from the SEIFEM and FUNGISCOPE registries

Table 1. Clinical characteristics and risk factors of 32 patients who developed invasive mucormycosis.

	N	%
Gender		
M	18	56
F	14	44

- 32 vaka (SEİFEM ve FUNGİSOPE)
- 27 (posakonazol + L-AmB)
- 5 (posakonazol + ABLC)
- **Posakonazol çoğunlukla kurtarma tedavisi olarak kullanılmış**
- Tedavi yanıtı= %56

Pagano L, Cornely O. Haematologica 2013

Posakonazol

- İdame tedavide
  - 4X200 mg/gün oral
  - Uygun serum ilaç konsantrasyonlarını elde etmek için öncesinde en az 5 gün primer tedavi ile birlikte verilmeli

AmB ve Kaspofungin Kombinasyon Tedavisi

Clin Infect Dis. 2008 Aug 1;47(3):364-71. doi: 10.1086/589857.

Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis.

Reed C[1], Bryant R, Ibrahim AS, Edwards J Jr, Filler SG, Goldberg R, Spellberg B.

⊕ Author information

Abstract

BACKGROUND: It has been axiomatic that echinocandins (e.g., caspofungin) are ineffective against mucormycosis. However, on the basis of preclinical data, we recently began treating rhino-orbital-cerebral mucormycosis (ROCM) with combination polyene-caspofungin therapy.

METHODS: To determine the impact of polyene-caspofungin therapy, ROCM cases identified by an International Classification of Diseases, Ninth Revision search were retrospectively reviewed to gather data on demographic characteristics, clinical history, and outcomes. The predefined primary end point was success (i.e., the patients was alive and not in hospice care) at 30 days after hospital discharge.

RESULTS: Forty ...were Hispanic, and 34 (83%) were diab...s (100% vs. 45%; Pp.02) and Kaplan-Mei...l with amphotericin B lipid complex had infe...ed with patients who received other p...r success (100% vs. 20%; Pp.009) and sur...enefit of combination therapy, compared with monotherapy, was most pronounced in patients with cerebral involvement (success rate, ...00% vs. 25%; Pp.01). In multivariate analysis, only receipt of combination therapy was significantly associated with improved outcomes (odds ratio, 10.9; 95%

Ekinokandinler in-vitro testlerde mukormikoziste etkisiz!!
Mevcut klinik veriler yetersiz

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2005, p. 721–727 Vol. 49, No. 2
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.2.721–727.2005

Caspofungin Inhibits *Rhizopus oryzae* 1,3-β-D-Glucan Synthase, Lowers Burden in Brain Measured by Quantitative PCR, and Improves Survival at a Low but Not a High Dose during Murine Disseminated Zygomycosis

Ashraf S. Ibrahim,[1,2]* Joel C. Bowman,[3] Valentina Avanessian,[1] Keturah Brown,[3] Brad Spellberg,[1,2] John E. Edwards, Jr.,[1,2] and Cameron M. Douglas[3]

Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles, Medical Center, Torrance,[1] and University of California, Los Angeles, School of Medicine, Los Angeles,[2] California, and Department of Human and Animal Infectious Disease Research, Merck Research Laboratories, Rahway, New Jersey[3]

Received 7 July 2004/Returned for modification 5 September 2004/Accepted 1 October 2004

Hiperbarik Oksijen

- Mukorales takımının üremesini inhibe eder (in vitro)
- Doku Hipoksisi ve asidozu azaltır
- Polienlerin oksidatif öldürme etkisini arttırır
- Anjiogenezi artırır ve iyileşmeyi hızlandırır

Tragiannidis A. Clin Microbiol İnfect 2009

- Diyabetik hastalarda daha yararlı

Tedavi süresi

- Hasta bazında değerlendirilmeli
- Klinik ve radyolojik tam iyileşme
- Altta yatan risk faktörleri düzelene kadar

Tedaviye devam edilmeli

REHBERLER

ECIL-5 (2013)

2013-Update of the ECIL Guidelines for Antifungal Therapy in Leukemia and HSCT Patients (ECIL-5)

CMI
CLINICAL MICROBIOLOGY AND INFECTION

ESCMID

Explore this journal >

ESCMID and ECMM PUBLICATIONS

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

O. A. Cornely ✉, S. Arikan-Akdagli, E. Dannaoui, A. H. Groll, K. Lagrou, A. Chakrabarti, F. Lanternier, L. Pagano, A. Skiada, M. Akova, M. C. Arendrup, T. Boekhout, A. Chowdhary, M. Cuenca-Estrella, T. Freiberger, J. Guinea, J. Guarro,

Sonuç

- **Erken Tanı!!!**
- Erken antifungal tedavi (ilk 5 gün)
- Kesin tanı için biyopsi!!!
- Multidisipliner yaklaşım