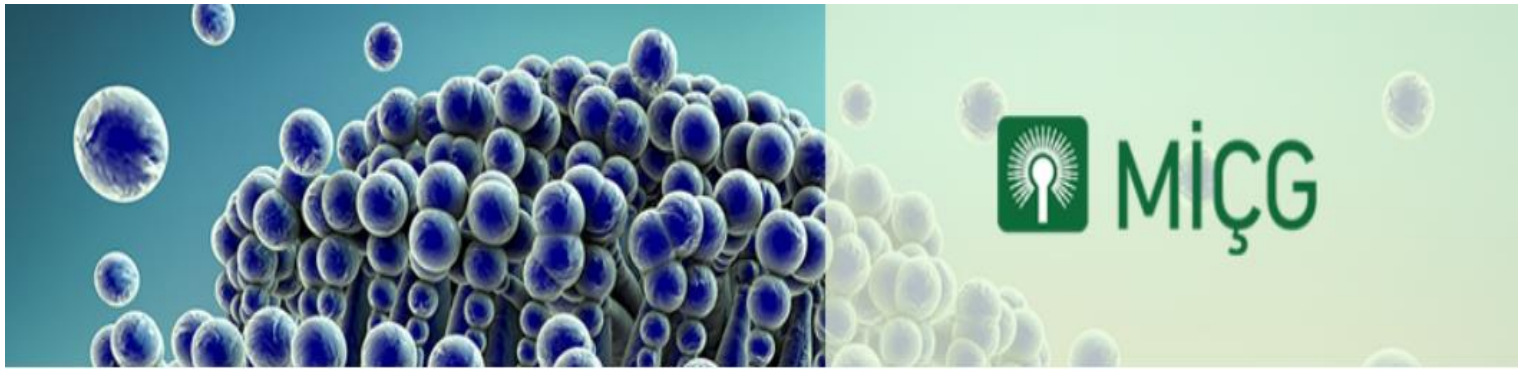


Hematoloji-Onkoloji Hastalarında İnvazif Fungal İnfeksiyonların Tedavisi

Dr. Süda TEKİN

Koç Üniversitesi Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Neler konuşulacak?

- ❖ Hematoloji-Onkoloji hastalarında fungal infeksiyonların önemi
- ❖ Antifungal tedavi
  - ✓ İnvazif kandidoz
  - ✓ İnvazif aspergilloz
  - ✓ İvazif mukormikoz
- ❖ Rehberler
- ❖ Soru & Katkı

PUBLISHED: 25 JULY 2017 | VOLUME: 2 | ARTICLE NUMBER: 17120

editorial

Stop neglecting fungi

Fungal pathogens are virtually ignored by the press, the public and funding bodies, despite posing a significant threat to public health, food biosecurity and biodiversity.

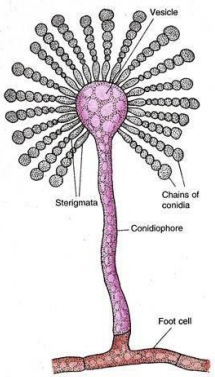
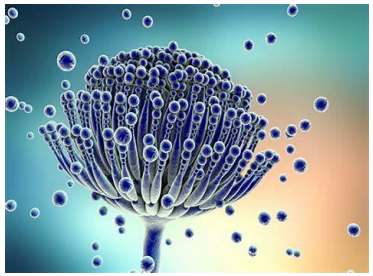
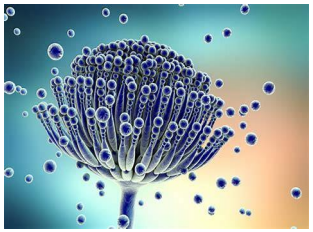


Fig. 10.3. *Aspergillus*. A mature conidiophore bearing sterigmata and chains of conidia.

Experts agree that fungal pathogens are a serious threat to human health, food biosecurity and ecosystem resilience, yet lack of funding translates into inadequate surveillance systems to monitor fungal disease incidence and antifungal drug resistance, which often rely on not-for-profit initiatives, such as the Global Action Fund for Fungal Infections (GAFFI; http://www.gaffi.org/). As highlighted in the World Health Organization (WHO) Global Report on Antimicrobial Resistance Surveillance[8], which devotes fewer than 10% of its pages to fungi, resources allocated for monitoring and reducing antifungal drug resistance are limited. Indeed, the WHO has no funded programmes specifically targeting fungal diseases, fewer than 10 countries have national surveillance programs for fungal infections, and fewer than 20 have fungal reference diagnostic laboratories.



İnvazif Fungal İnfeksiyon



- İFİ'lere bağlı mortaliye artmaktadır
- ABD verilerine göre İFİ ölümcül infeksiyonlar arasında;
  - ✓ Kandidemi yoğun bakım ünitelerinde **5. ölüm** nedeni
  - ✓ 1–8 olgu 100 000/ülkede yaşayanlar

Atfedilen mortalite

❖ Erişkinlerde %15–35

❖ Yenidoğanlarda %10–15

Allo KİT	**% 15-25**
AML	%10-15
ALL	%5-10
Otolog KİT	%2-6

Bouza E, et al. *Int J Antimicrob Agents.* 2008; 32: S87-1.
Diagn Microbiol Infect Dis. 2012; 73: 45–8.

İtalya, SEIFEM Çalışması 2004

Retrospektif kohort 1999-2003

N = **11 802** hematolojik malignite N = **3228** erişkin KİT

Malignite	IFI insidansı	Küf insidansı	Maya İnsidansı
AML	%12	%7.9	%4.4
ALL	%6.5	%4.3	%2.2
Allojeneik KİT	%7.8	%6.7	%1.1
KML	%2.5	%2.3	%0.2
KLL	%0.5	%0.4	%0.1
NHL	%1.6	%0.9	%0.7
HH	%0.7	%0.35	%0.35
MM	%0.5	%0.3	%0.2
Otolog KİT	%1.2	%0.4	%0.8

Panago L et al. *Haematologica*. 2006; 91:1068-75.

Fungemia in hematological malignancies: SEIFEM-2015 survey.

Eur J Clin Invest. 2019 Feb 8:e13083. (Epub)

- Ocak 2011 – Aralık 2015
- İtalya, hematoloji, **28 erişkin** ile **6 pediatri** klinikleri

215 İFİ atağı =>

- ✓ 17 hasta (**%8**) küf mantarı

Mortalite %70

Mortalite %39

- ✓ 198 hasta (**%92**) maya, 174 (**%81**)'ünde *Candida* spp.

***Kandidozda kateter infekteyse çıkartmak gerekli ve önemli**

Open Forum Infectious Diseases

MAJOR ARTICLE

Epidemiology and Clinical Features of Invasive Fungal Infection in a US Health Care Network

Brandon J. Webb,[1,2] Jeffrey P. Ferraro,[3,4] Susan Rea,[3] Stephanie Kaufusi,[3,5] Bruce E. Goodman,[3,5] and James Spalding[6]

- 3154 hastada **3374 IFI** epizotu
- Ortalama insidans **27.2/100 000** olgu/hasta yılı
- Artış **0.24 olgu/100 000** (*P* = 0.21).
- **Kandidoz** en sık, **%55**.

IFI in a US Health Network. 2018

Open Forum Infectious Diseases

MAJOR ARTICLE

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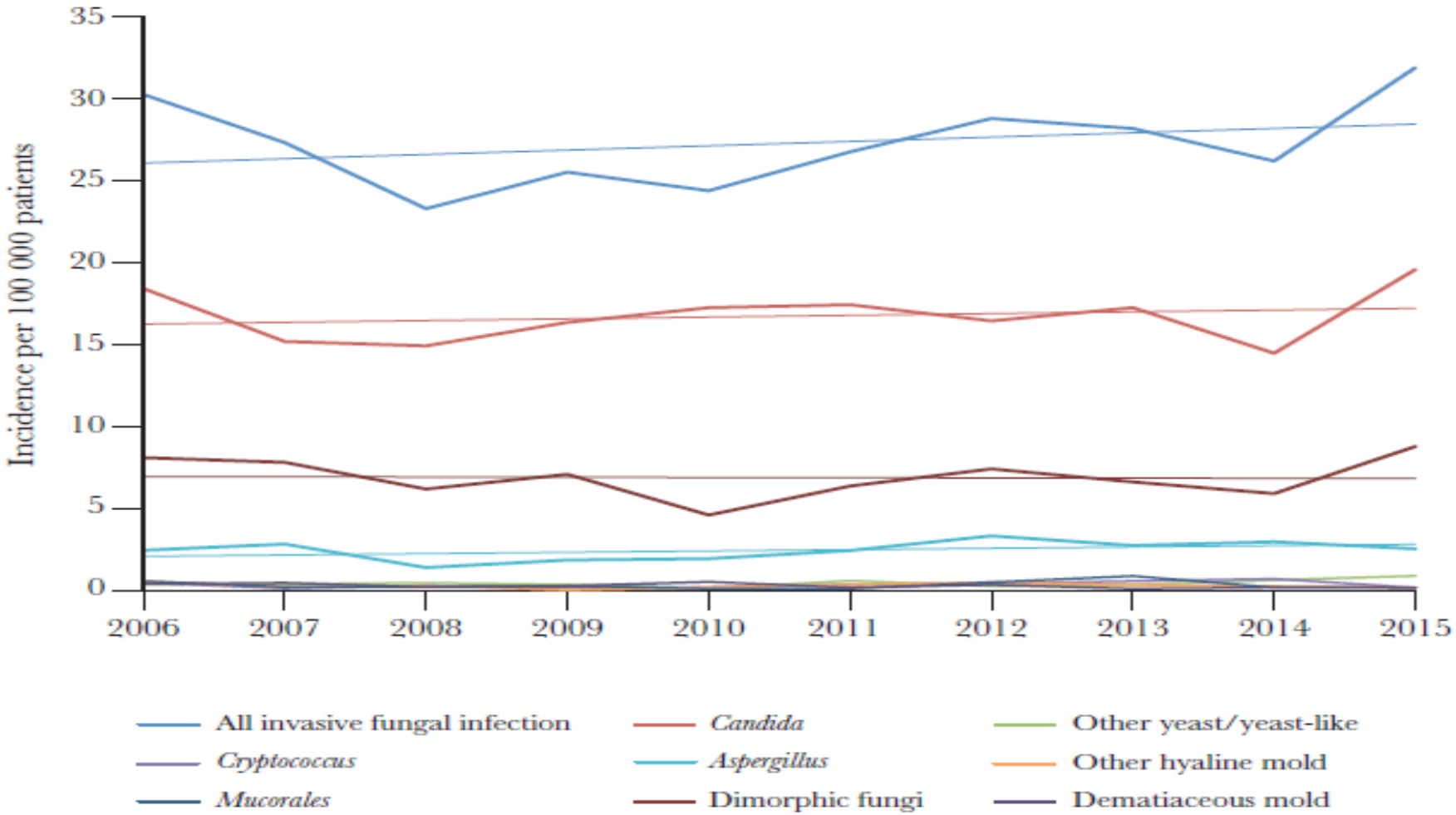
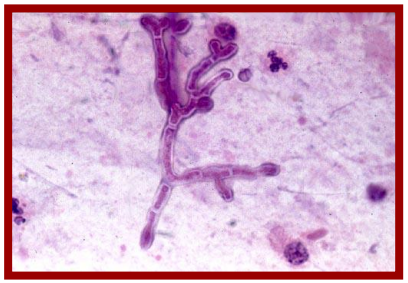
Brandon J. Webb,[1,2] Jeffrey P. Ferraro,[3,4] Susan Rea,[3] Stephanie Kaufusi,[3,5] Bruce E. Goodman,[3,5] and James Spalding[6]



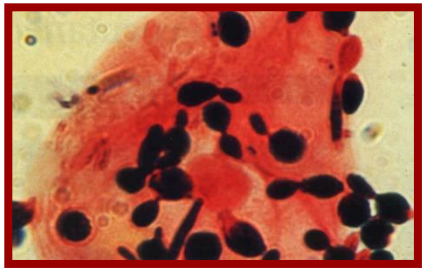
IFI in a US Health Network. 2018

Güncel epidemiyoloji



- Mantar infeksiyonları…

Invazif kandidoz
Invazif aspergilloz
PCP (*P. jiroveci)*
Cryptococcosis
Zygomycosis
Scedosporium infeksiyonu
Fusarium infection
Histoplasmosis
Penicilliosis
Coccidioidomycosis
Blastomycosis



Richardson M, Lass-Flörl. *Clin Microbiol Infect.* 2008;14 :5-24.
Warnock D. *Jpn J Med Mycol*. 2007;48:1-12.

İnvazif fungal infeksiyonlar önemlidir!

Olumsuz konak koşulları

•Düşük klinik yanıt oranları
•Yüksek mortalite

Dirençli cins ve suşlar

Erken tanıda zorluklar

Antifungal tedaviye suboptimal yanıt

Richardson. *JAC* 2005; 56(S1): i5,
Bille et al. *Curr Opin Infect Dis* 2005; 18: 314

İnvazif fungal infeksiyonlarda klinik belirti ve bulgular

Organ	Belirti ve Bulgular	Tanı
Deri	Papül, nodül, püstül, vezikül, ülser, selülit, yüzeysel granülomlar ve plaklar, abse	Akut disemine kandidoz, disemine aspergilloz veya fuzaryoz, kriptokokoz
Sinonazal	Yüzde ağrı, epistaksis, nazal konjesyon, ülserler, nekrotik skar	İnvazif aspergilloz, invazif zigomikoz
Oral kavite	Eritemli veya beyaz noktalanma, ülserler, nekrotik skar	Oral kandidoz, invazif aspergilloz, invazif zigomikoz
Göğüs	Plöritik ağrı, dispne, kuru öksürük, hemoptizi, göğüs ağrısı	İnvazif aspergilloz ve diğer küf infeksiyonları, PCP, pnömoni
Göz	Koryoretinit/endoftalmit, fundoskopide ‘pamuk atılmış’ benzeri lezyonlar	Oküler veya akut disemine kandidoz
MSS	Baş ağrısı, meningismus, fokal nörolojik defisit, nöbetler	Kriptokoka bağlı meningoensefalit, AT; Kandida menenjiti, küf absesi

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İFİ Yönetim-Tanı

Tanıyabiliyor muyuz?

- **Konak faktörleri** - Yüksek risk?
- **Görüntüleme** - Patojen hangisi?
- **Laboratuvar testleri**
  - Kan kültürü
  - Diğer kültürler/mikroskopi
  - Biyobelirteçler

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İFİ Yönetim-Tanı

Tanıyabiliyor muyuz?

- **Konak faktörleri** - Yüksek risk?

- **Görüntüleme** – Patojen hangis

Host Risk Factors for Invasive Aspergillosis

Probability

- Allogeneic HSCT
- Pmn<500 + hematologic cancer, autologous HSCT, aplastic anemia, MDS
- Solid organ transplant, AIDS or high-dose corticosteroids

estleri

n kültürü

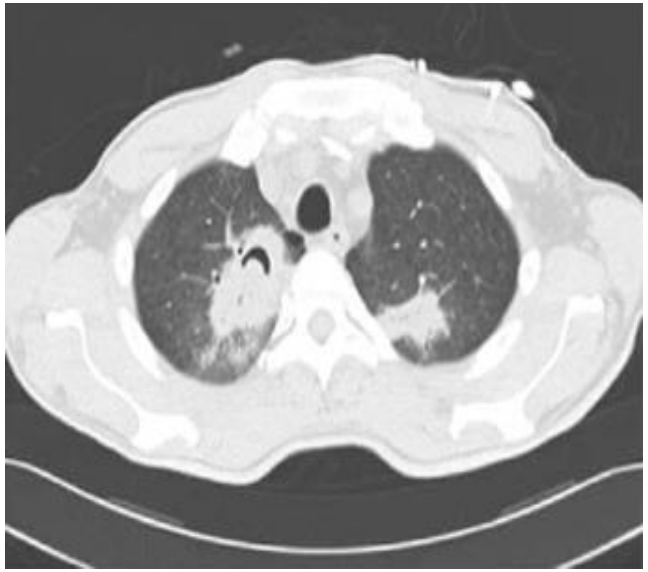
er kültürler/mikrosko

obelirteçler

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İFİ Yönetim-Tanı

Tanıyabiliyor muyuz?



- **Konak faktörleri** - Yüksek risk?
- **Görüntüleme** – Patojen hangisi?
- **Laboratuvar testleri**
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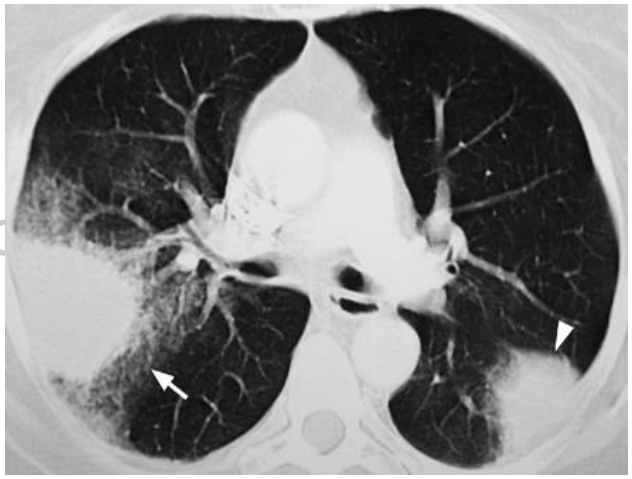
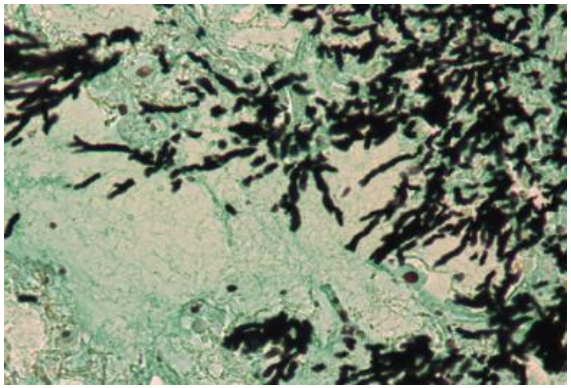
  - biyobelirteçler



İFİ Yönetim-Tanı

Tanıyabiliyor muyuz?

- **Konak faktörleri** - Yüksek risk?
- **Görüntüleme** – Patojen



- **Laboratuvar testleri**
  - Kan kültürü
  - Diğer kültürler/mikroskopi
  - Biyobelirteçler

Clinical Infectious Diseases Advance Access published December 16, 2015
IDSA GUIDELINE

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

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

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

Rehberler

Endüstrinin etkisi

Tedavi

Liderler

Yönetim?

Yerel veriler

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Antifungal Yönetim nedir?

"The right **ANTIFUNGAL** for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients"

www/cdc.gov/getsmart/healthcare/inpatient-stewardship

Yönetim ekibi

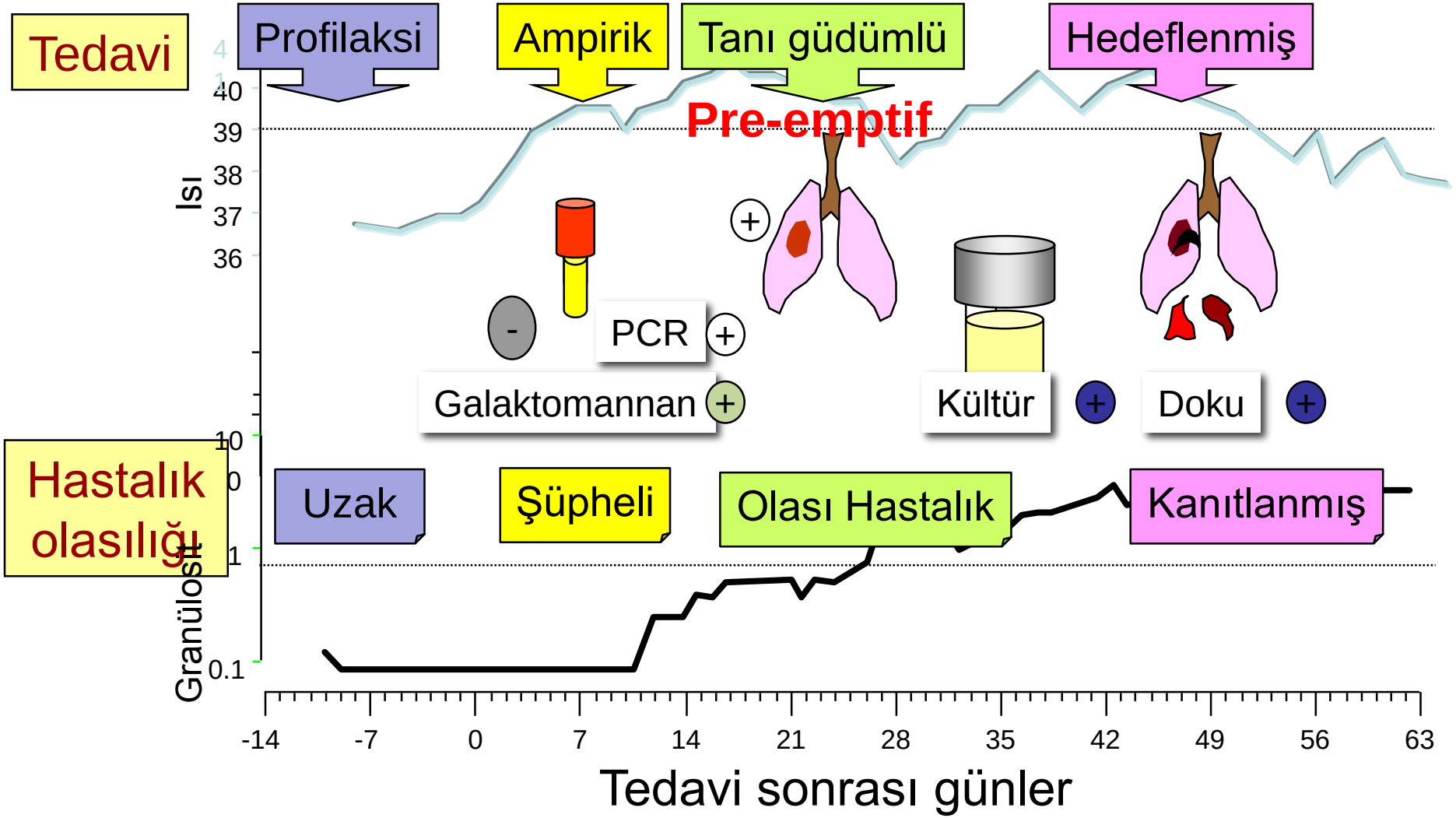
- Farmakolog
- EHU / EH**KM**U
- Hem-Onkolog
- Veriler (sürveyans)

Hematoloji-Onkoloji Hastalarında İFİ'de İlaç Seçiminde Kritik Faktörler

- Epidemiyoloji ve direnç
- Antifungal profilaksi
- Tanı
- İlaç sağlanması/olanaklar
- İlaç etkinliği & toksisitesi & oral kullanılabilirliği
- İlaç etkileşimleri
- Maliyet
- Rehberler; Lokal & evrensel

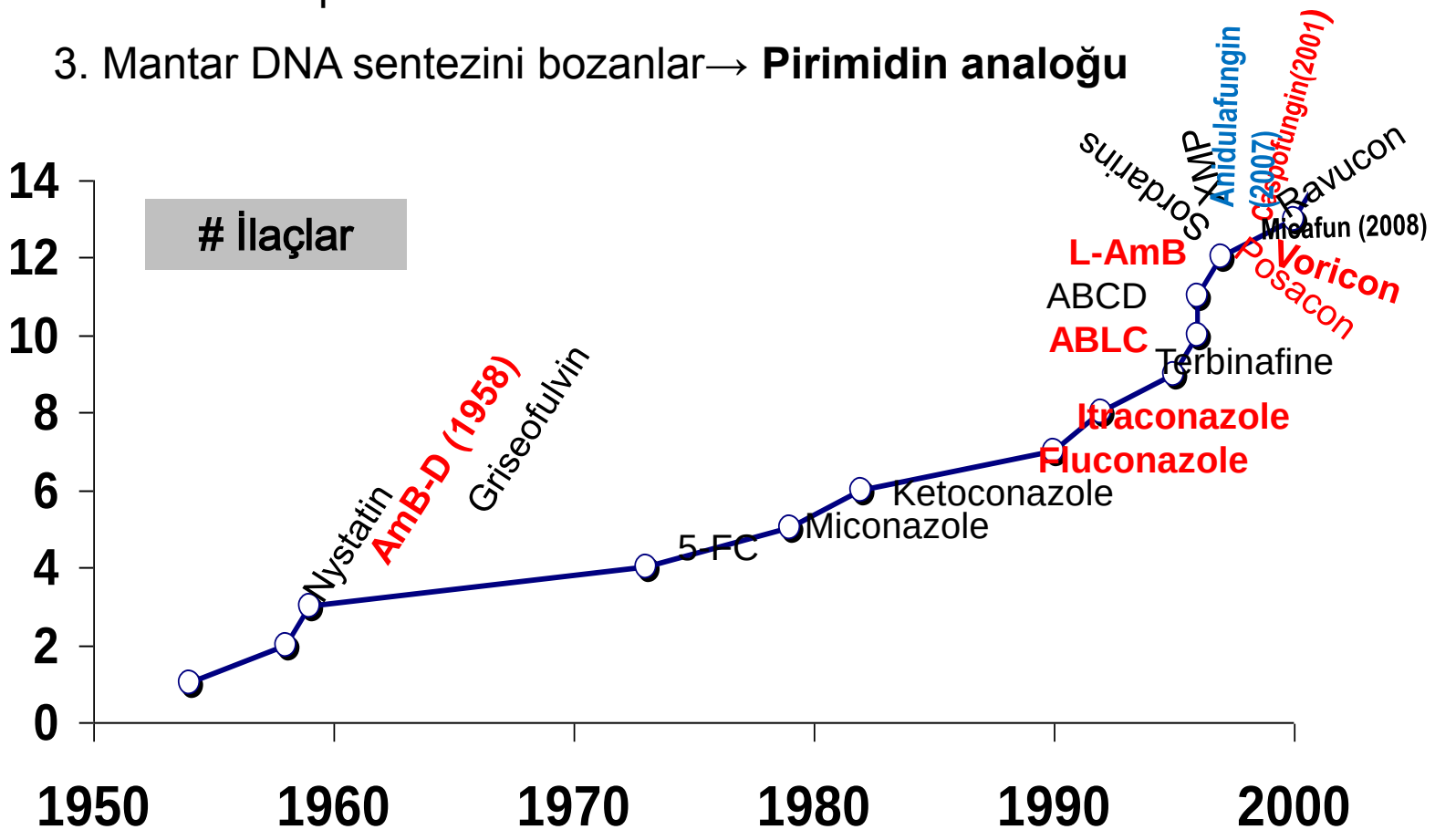
Kalıplaşmış davranış, veri yetersizliğiyle beslenir!

Antifungal: Ne Zaman?



Antifungal Tedavi

1. Mantar duvar sentezini bozanlar→ **Ekinokandinler**
2. Mantar sitoplazmik membranını bozanlar→ **Polienler / Triazoller**
3. Mantar DNA sentezini bozanlar→ **Pirimidin analoğu**



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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Antifungal Tedavi

- **Azoller, Polienler, Ekinokandinler**
- Seçim:
  - Konakçı immün durumu
  - Karaciğer - böbrek fonksiyonları
  - Tolerabilite
  - Önceki tedaviler?

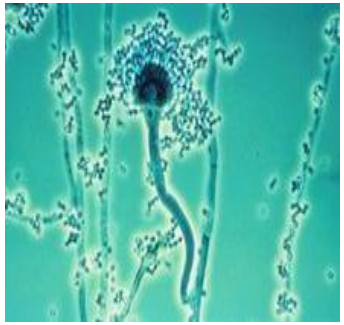
- **Başlangıç Tedavisi**

- **Kurtarma Tedavisi**

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Hematoloji-Onkoloji Hastalarında İFİ

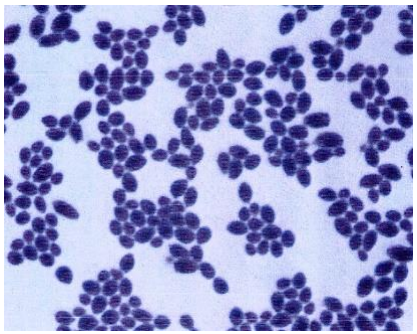
- İnvazif kandidoz
- İnvazif aspergilloz
- İnvazif zigomikoz (mukormikoz)



MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Hematoloji-Onkoloji Hastalarında İFİ

- **İnvazif kandidoz**
- **İnvazif aspergilloz**
- **İnvazif zigomikoz (mukormikoz)**



MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Olgu 1

- 59 yaşında, kadın
- Yaygın Non-Hodgkin **Lenfoma** (Büyük Hücreli)
- **DM**
- **KİT** sonrasında **nötropenik ateş**
- **SVK** mevcut
- **CRP**: **342** mg/dl (N: 0-5), **prokalsitonin: 8**
- Piperasilin-tazobaktam 4x4.5 g iv başlandı
- Kan ve diğer kültürleri alındı
- İdrar kültürü
- ?

Morganella morganii 100000 kob/ml
Dirençli : Ampisilin, Gentamisin, Nitrofurantoin, Sefuroksim
Hassas : Amikasin, Meropenem, Piperasillin & Tazobaktam
Orta Derece Hassas : Ciprofloksasin

Ateşi devam edince 48. saatte vankomisin 2x1 g eklendi

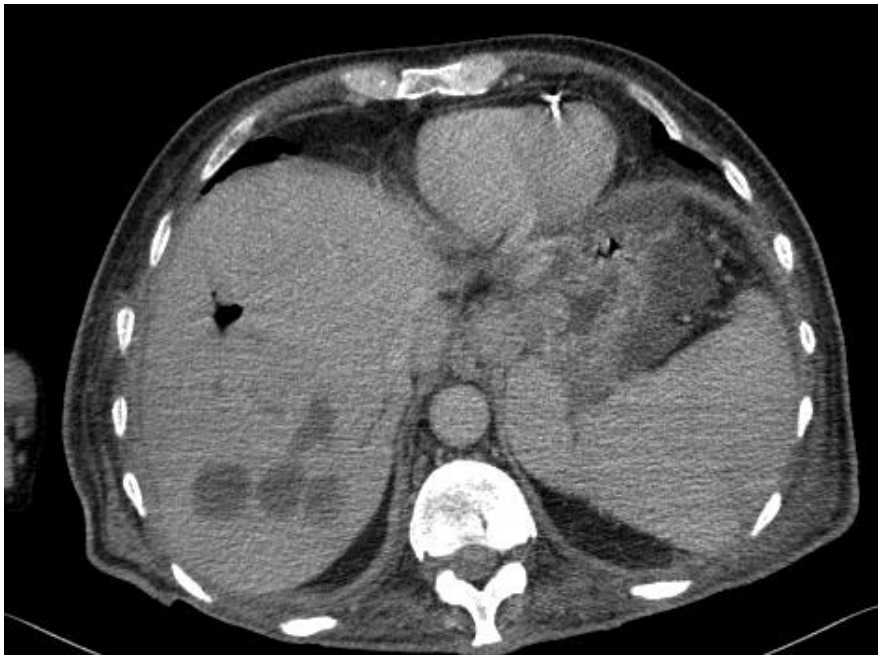
Halen ateşli 5. gün ve nötropenik

- ✓ Takiplerinde oral mukozit var
- ✓ Antifungal eklendi
- ✓ Mikafungin **1x150** mg İV

(Azol prof almış hasta)

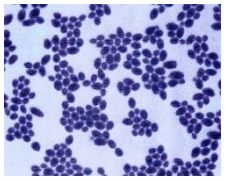
❖ Kan kültürü ve SVK kültür=> ***Candida krusei***

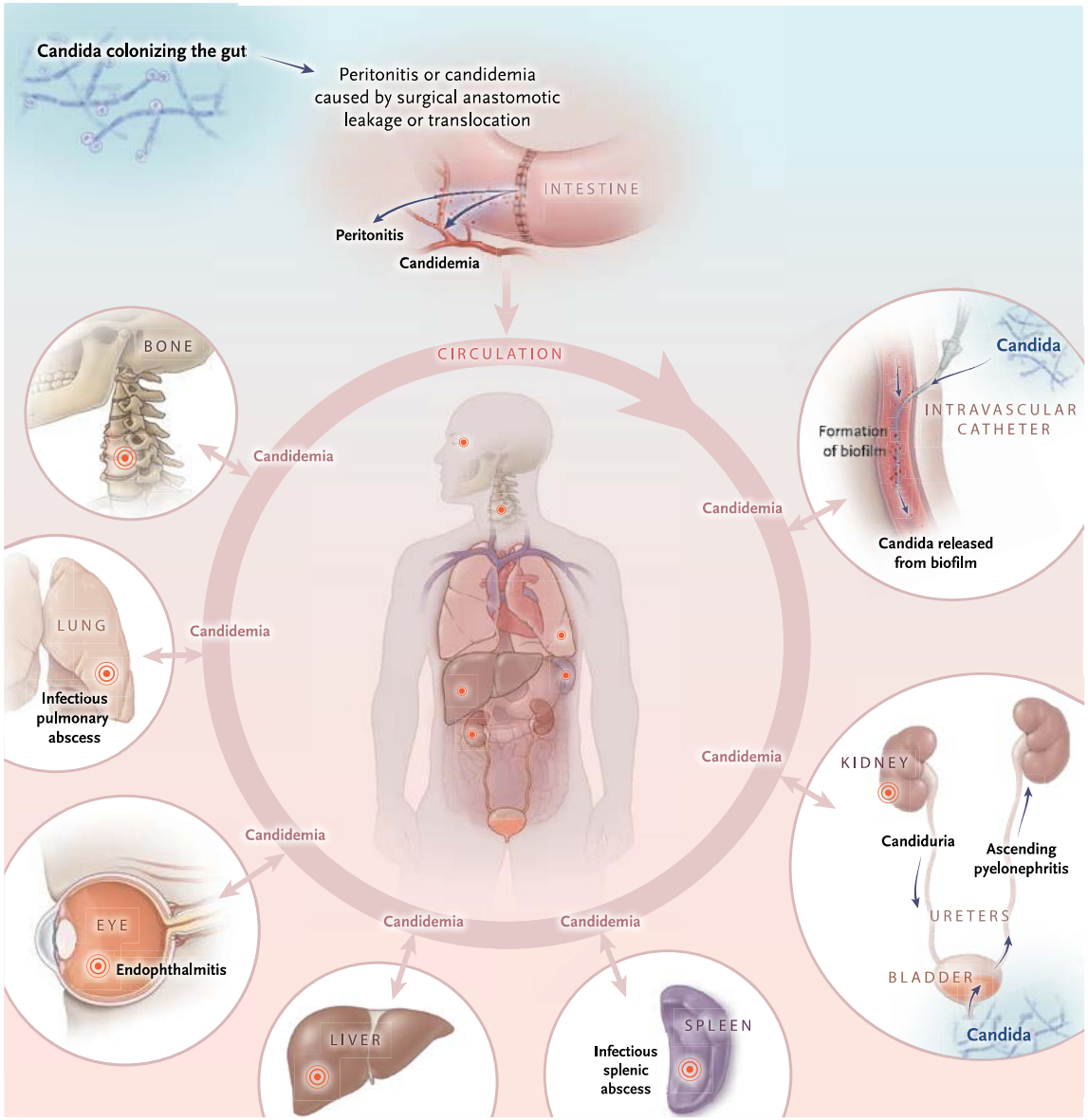
Dirençli : Flucytosine, Flukanazol
Hassas : Kaspofungin, Mikafungin, Vorikonazol
Orta Derece Hassas : Amfoterisin B



Invasive Candidiasis

Bart Jan Kullberg, M.D., Ph.D., and Maiken C. Arendrup, M.D., Ph.D.





İnvazif kandidoz:

Kandidemi ve «deep-seated» doku kandidozu

Fatalite %40

N Engl J Med. 2015;373:1445-56

Table 1 *Candida* spp. isolates presenting both resistant and non-wild-type phenotypes according to applied CLSI BPs and ECVs

Strain code	Year	Species identification	FL MIC (mg/L)	VOR MIC (mg/L)	PZ MIC (mg/L)	IZ MIC (mg/L)	CAS MIC (mg/L)	MCF MIC (mg/L)
1835	2009	*Candida*	32	0.25				
1729	2009							
1719	2009							
2362	2009					16		
2419	2009					> 16	0.25	
591	2010	*Candida orthopsilosis*	16	0.5				
1064	2014	*Candida glabrata*	16	0.5				0.25

BP break point; *ECV* epidemiological cut-off value; *CLSI* Clinical and Laboratory Standards Institute; *FL* fluconazole; *MF* micafungin; *VOR* voriconazole; *PZ* posaconazole; *IZ* itraconazole; *CAS* caspofungin; *MCF* micafungin

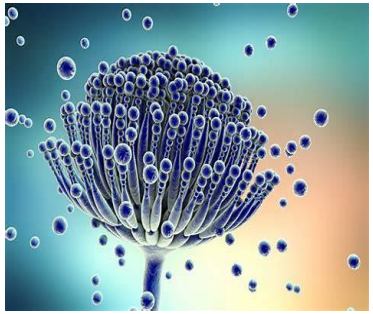
Kendi ünitenizin lokal verilerini bilin ve tedavi yönetimini buna göre karar verin.

Sonuç:

Mycopathologia. 2018.

C. glabrata **%23.5'i flukonazole dirençli**,
C. parapsilosis %5.08 flukonazole dirençli
C. albicans, C. tropicalis and *C.lusitaniae* isolatlarında flukonazole direnci saptanmamış
C. glabrata 1(%5.8) isolatı ekinokandin dirençli

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU



İnvazif Kandidoz Rehberler

I. 2016 IDSA

II. 2017 ECIL-6

III. Yeni çalışmalar

I. IDSA Management of Candidiasis. *CID.* 2016:62

II. Tissot. F, et al. *Haematologica* 2017;102:433-44.

Clinical Infectious Diseases
IDSA GUIDELINE

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

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

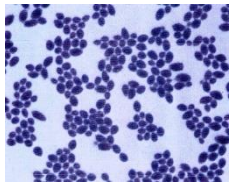
- Kandida türleri İK sonrası önemli mortalite ve morbidite nedeni
- **>%90** invazif hastalıktan;
- *C. albicans, C. glabrata C. tropicalis, C. parapsilosis, C. krusei* sorumlu

IDSA Management of Candidiasis. *CID.* 2016:62

Clinical syndrome	IDSA 2016 [82]
Candidemia, non-neutropenic patient	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): *strongly recommended*; *high-quality evidence* Fluconazole 800 mg (12 mg/kg) then 400 mg/d: *strongly recommended*; *high-quality evidence*[a] Lipid formulation AMB (3–5 mg/kg/d): *strongly recommended*; *high-quality of evidence*[b]
Candidemia, neutropenic patient	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): *strongly recommended*; *moderate-quality evidence* Fluconazole 800 mg (12 mg/kg) then 400 mg/d: *weakly recommended*; *low-quality evidence*
Chronic disseminated candidiasis (hepatosplenic)	Lipid formulation AMB (3–5 mg/kg/d) or an echinocandin for several weeks followed by oral fluconazole 400 mg/d: *strongly recommended*; *low-quality evidence*
Candida endocarditis: native valve	Lipid formulation AMB (3–5 mg/kg/d) ± flucytosine 25 mg/kg 4 times/d or high dose echinocandin (Caspofungin 150 mg/d; Micafungin 150 mg/d; Anidulafungin 200 mg/d): *strongly recommended*; *low-quality evidence*
Candida endocarditis: prosthetic valve	Same anti-fungal regimens: *strongly recommended*; *low-quality evidence* Chronic suppressive anti-fungal therapy with fluconazole (400–800 mg daily): *strongly recommended*; *low-quality evidence*
Candida osteomyelitis	Fluconazole 400 mg/d for 6–12 months or an echinocandin for at least 2 weeks followed by fluconazole 400 mg/d for 6–12 months: *strongly recommended*; *low-quality evidence*
Candida chorioretinitis without vitritis	Fluconazolo 800 mg/d then 400–800 mg/d or voriconazole 400 mg × 2/d then 300 mg × 2/d for 4–6 weeks: *strongly recommended*; *low-quality evidence*
Candida chorioretinitis with vitritis	Same as above plus intravitreal injection (AMB deoxycholate 5–10 μg/0.1 mL sterile water or voriconazole 100 μg/0.1 mL sterile water): *strongly recommended*; *low-quality evidence*
Central nervous system candidiasis	Liposomal AMB 5 mg/kg) ± flucytosine 25 mg/kg 4 times/d followed by fluconazole 400–800 mg/kg/d: *strongly recommended*; *low-quality evidence*

IDSA Management of Candidiasis. *CID.* 2016: 62.

Nötropenik olmayan hastada kandidemi



Clinical Infectious Diseases
IDSA GUIDELINE

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

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

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

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Keywords. candidemia; invasive candidiasis; fungal diagnostics; azoles; echinocandins.

EXECUTIVE SUMMARY

Background

Invasive infection due to *Candida* species is largely a condition associated with medical progress, and is widely recognized as a major cause of morbidity and mortality in the healthcare environment. There are at least 15 distinct *Candida* species that cause human disease, but >90% of invasive disease is caused by the 5 most common pathogens, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Each of these organisms has unique virulence potential, antifungal susceptibility, and epidemiology, but taken as a whole, significant infections due to these organisms are generally referred to as invasive candidiasis. Mucosal *Candida* infections—especially those involving the oropharynx, esophagus, and vagina—are not considered to be classically invasive disease, but they are included in these guidelines. Since the last iteration of these guidelines in 2009 [1], there have been new data pertaining to diagnosis, prevention, and treatment for proven or suspected invasive candidiasis, leading to significant modifications in our treatment recommendations.

Summarized below are the 2016 revised recommendations for the management of candidiasis. Due to the guideline's relevance to pediatrics, the guideline has been reviewed and endorsed by the American Academy of Pediatrics (AAP) and the Pediatric Infectious Diseases Society (PIDS). The Mycoses Study Group (MSG) has also endorsed these guidelines. The panel followed a guideline development process that has been adopted by the Infectious Diseases Society of America (IDSA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong) [2] (Figure 1). [3] The guidelines are not intended to replace clinical judgment in the management of individual patients. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found in the full text of the guideline.

I. What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy *(strong recommendation; high-quality evidence)*.
2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species *(strong recommendation; high-quality evidence)*.
3. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant *Candida* isolates. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and among those who have infection with *C. glabrata* or *C. parapsilosis* *(strong recommendation; low-quality evidence)*.

Received 28 October 2015; accepted 2 November 2015.

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Clinical Infectious Diseases®

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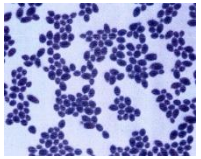
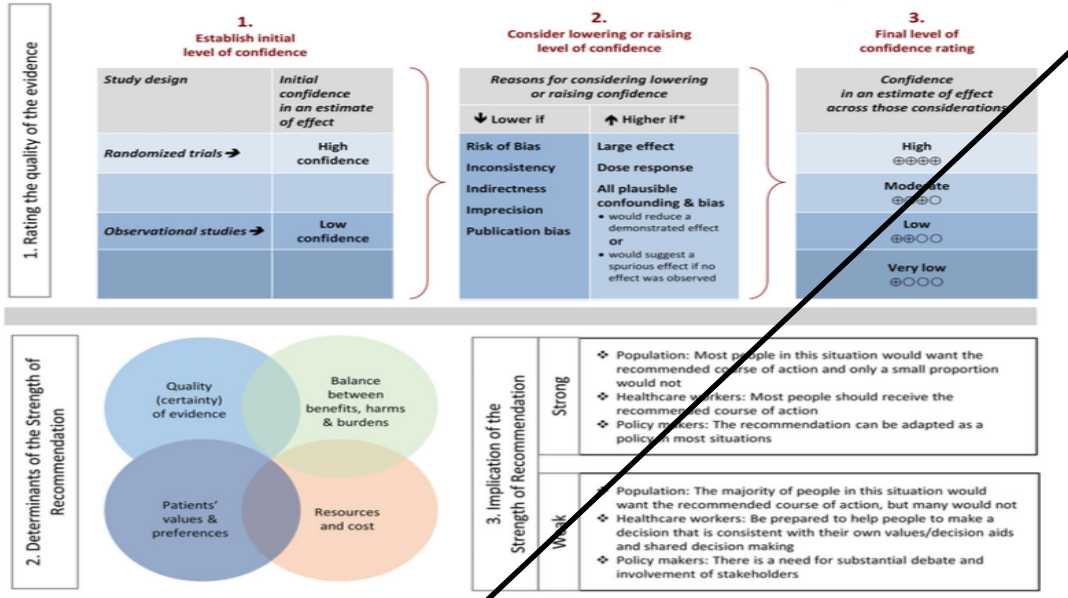
1. Başlangıç tedavisi olarak bir **ekinokandin** önerilir.
(Güçlü öneri; yüksek nitelikli kanıt)

IDSA Management of Candidiasis. *CID.* 2016:62

Nötropenik olmayan hastada kandidemi





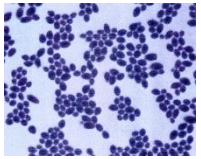
igure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development nd Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network) [3].

4. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, *C. albicans*), and have negative repeat blood cultures following initiation of antifungal therapy *(strong recommendation; moderate-quality evidence)*.
5. For infection due to *C. glabrata*, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200–300 (3–4 mg/kg) twice daily should only be considered among patients with fluconazole-susceptible or voriconazole-susceptible isolates *(strong recommendation; low-quality evidence)*.
6. Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents *(strong recommendation; high-quality evidence)*.
7. Transition from AmB to fluconazole is recommended after 5–7 days among patients who have isolates that are susceptible to fluconazole, who are clinically stable, and in whom repeat cultures on antifungal therapy are negative *(strong recommendation; high-quality evidence)*.
8. Among patients with suspected azole- and echinocandin-resistant *Candida* infections, lipid formulation AmB (3–5 mg/kg daily) is recommended *(strong recommendation; low-quality evidence)*.
9. Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily is effective for candidemia, but offers little advantage over fluconazole as initial therapy *(strong recommendation; moderate-quality evidence)*. Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to *C. krusei* *(strong recommendation; low-quality evidence)*.
10. All nonneutropenic patients with candidemia should have a dilated ophthalmological examination, preferably performed by an ophthalmologist, within the first week after diagnosis *(strong recommendation; low-quality evidence)*.
11. Follow-up blood cultures should be performed every day or every other day to establish the time point at which

2. Başlangıç antifungal tedavisi sonrası ekinokandinden **flukonazole geçiş (genellikle 5-7** gün sonra), klinik olarak stabil, tekrarlanan kan kültürü negatif olan hastalarda ve flukonazole duyarlı izolatlarda ve önerilir. (Güçlü öneri, orta nitelikte kanıt)

IDSA Management of Candidiasis. *CID.* 2016:62

IDSA 2016: Nötropenik hastalar



- Başlangıç tedavisi **ekinokandin**
  - Daha düşük seçenek: amfoterisin B (lipid)
  - Durumu kritik olmayanlarda flukonazol: daha önce flukonazol maruziyeti yoksa.

- ***C krusei:*** **Ekinokandin**, amfoterisin B (lipid), veya voriconazole

- Metastatik komplikasyonlarda: minimum tedavi süresi eradikasyonu dökümente ettikten **sonra 2 hafta**
- Funduskopik muayene: nötropeniden çıktıktan 1 hafta sonra
- Kateter çıkarımı olguya özgü değerlendirilmelidir.

IDSA Management of Candidiasis. *CID.* 2016:62

GUIDELINE ARTICLE

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

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

[1]Infectious Diseases Service, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland; [2]Division of Haemato-Oncology, St Bartholomew's Hospital and Blizard Institute, Queen Mary University, London, UK; [3]Hematology, Catholic University of Sacred Heart, Roma, Italy; [4]School of Medicine, European University Cyprus, Engomi, Cyprus; [5]Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital, Münster, Germany; [6]1st Department of Medicine, University of Athens, Greece; [7]Division of Hygiene and Medical Microbiology, Medical University of Innsbruck, Austria; [8]University of Genova (DISSAL), Infectious Disease Division, IRCCS San Martino-IST, Genova, Italy and [9]Oncology and Hematology, Hôpitaux Universitaires de Strasbourg and Université de Strasbourg, France

EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

EORTC
EBMT
ELN
ICSH

Haematologica 2017
Volume 102(3):433-444

ECIL-6; İnvazif kandidozda antifungal tedavi

	Overall population	Hematologic patients
Antifungal therapy		
Micafungin[a]	A I	A II
Anidulafungin	A I	A II[b]
Caspofungin	A I	A II
Liposomal amphotericin B	A I	A II
Amphotericin B lipid complex	B II	B II
Amphotericin B colloidal dispersion	B II	B II
Amphotericin B deoxycholate[c]	C I	C II
Fluconazole[d,e]	A I	C III
Voriconazole[d]	A I	B II
Catheter removal[f]	A II	B II

❖Ampirik olarak başka bir antifungal başlanmışsa;

✓ **Nötropenik değilse, s**tabilse, kan kültüründe üreme olmamışsa,

✓ Kandida suşu **flukonazole duyarlıysa**, 10 gün içinde **flukonazole** geçilebilir (''step down strateji'')

❖ Dökümante edilmiş kandidemide toplam tedavi **süresi ilk alınan negatif kan kültüründen** sonra **14 gün**

Tissot F, et al. ECIL 6. *Haematologica.* 2017; 102: 433-44.

ECIL-6; İnvazif kandidozda antifungal tedavi

Kandida türleri	Genel popülasyon	ÖG/KK	Hematoloji hastaları	ÖG/KK
C. albicans	Ekinokandinler	AI	Ekinokandinler	AII
	Flukonazol	AI	Flukonazol	CII
	Lipozomal AmB	AI	Lipozomal AmB	BII
	AmB lipid kompleksi	AII	AmB lipid kompleksi	BII
C. glabrata	Ekinokandinler	AI	Ekinokandinler	AII
	Lipozomal AmB	BI	Lipozomal AmB	BII
	AmB lipid kompleksi	BII	AmB lipid kompleksi	BII
C. krusei	Ekinokandinler	AII	Ekinokandinler	AIII
	Lipozomal AmB	BI	Lipozomal AmB	BII
	AmB lipid kompleksi	BII	AmB lipid kompleksi	BII
Oral devamı	Vorikonazol	BI	Vorikonazol	CII
C.parapsilosis	Flukonazol	AII	Flukonazol	AIII
	Ekinokandinler	BII	Ekinokandinler	BIII

Tissot F, et al. ECIL 6. *Haematologica.* 2017; 102: 433-44.

Received: 6 June 2017 | Revised: 11 January 2018 | Accepted: 13 January 2018

DOI: 10.1111/myc.12748

ORIGINAL ARTICLE

WILEY mycoses

Efficacy of micafungin for the treatment of invasive candidiasis and candidaemia in patients with neutropenia

Pranatharthi Chandrasekar[1] | Bhawna Sirohi[2] | Nita L. Seibel[3] |

*Mikafungin 100 mg & L-AmB 2mg/kg/g

*Mikafungin 100/150 mg & kaspofungin 70 mg ilk gün, devamı 50 mg/g

Parameter, n (%)	Neutropenia (n = 77)	Non-neutropenic (n = 608)
Type of infection		
Candidaemia	70 (90.9)	512 (84.2)
Invasive candidiasis	7 (9.1)	95 (15.6)
Infecting *Candida* spp.[a]		
C. tropicalis	31 (40.3)	109 (17.9)
C. albicans	19 (24.7)	295 (48.2)
C. krusei	15 (19.5)	14 (2.3)
C. glabrata	8 (10.4)	84 (13.8)
Other *Candida* spp.	5 (6.5)	44 (7.2)
C. parapsilosis	2 (2.6)	102 (16.8)

	Neutropenia (n = 77)	Non-neutropenic (n = 608)	*P* Value[a]
Overall mortality, n/n (%)	36/77 (46.8)	218/608 (35.9)	.0790
Day 28 mortality, n/n (%)	30/74 (40.5)	142/574 (24.7)	.0051
Day 84 mortality, n/n (%)	35/49 (71.4)	206/340 (60.6)	.1591

Received: 6 June 2017 | Revised: 11 January 2018 | Accepted: 13 January 2018
DOI: 10.1111/myc.12748

ORIGINAL ARTICLE

WILEY mycoses

Efficacy of micafungin for the treatment of invasive candidiasis and candidaemia in patients with neutropenia

Pranatharthi Chandrasekar[1] | Bhawna Sirohi[2] | Nita L. Seibel[3] |

***Mikafungin** & **L-AmB**
***Mikafungin** & **kaspofungin**

- Nötropeni süresi veya *Candida* türü mikafunginin genel başarı hızını etkilememiş.
- Mikafungin invazif kandidoz/kandidemide nötropeni süresinden bağımsız olarak etkilidir.
- Nötropenik olmayanlarda başarı elbette çok daha yüksektir.

Infect Dis Ther
https://doi.org/10.1007/s40121-019-0236-3

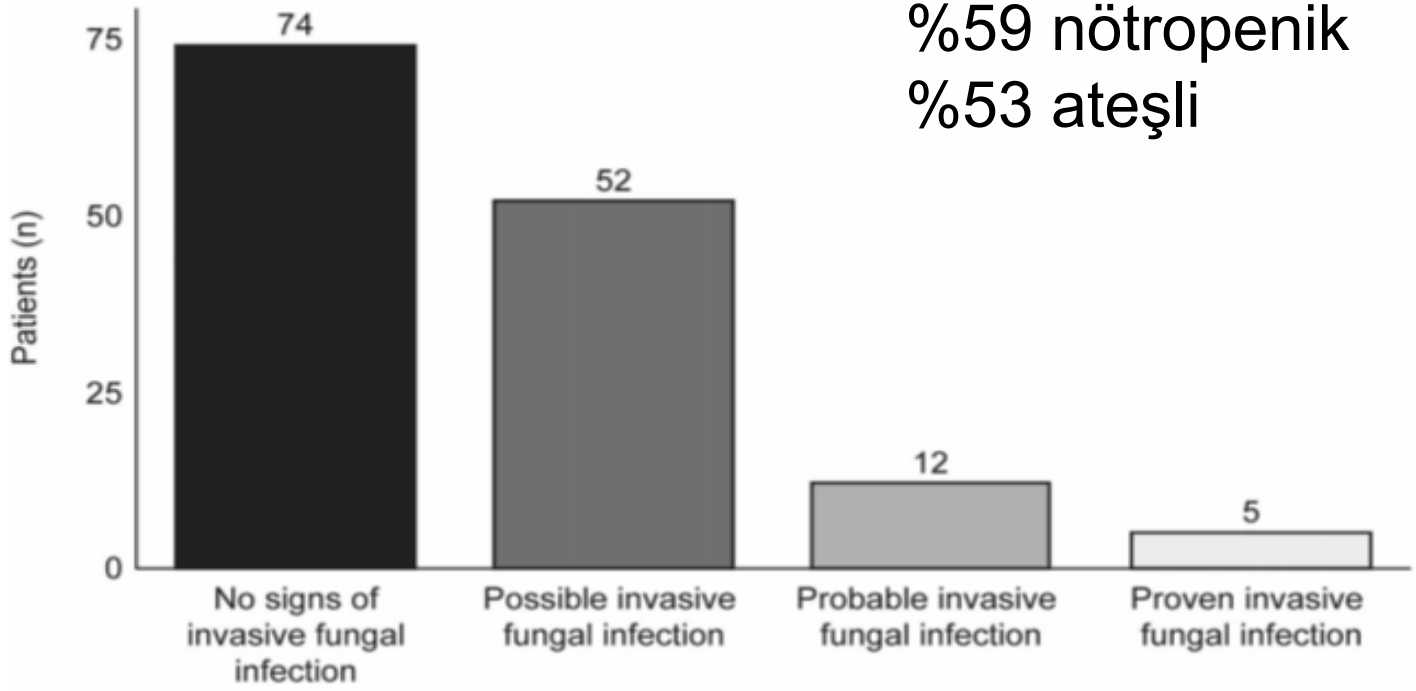
Published online: 14 February 2019

ORIGINAL RESEARCH

Effectiveness and Safety of Micafungin in Managing Invasive Fungal Infections among Patients in Greece with Hematologic Disorders: The ASPIRE Study

Maria Kotsopoulou · Christina Papadaki · Konstantinos Anargyrou ·

Toplam **143** hematoloji hastası
%59 nötropenik
%53 ateşli



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ORIGINAL RESEARCH

Effectiveness and Safety of Micafungin in Managing Invasive Fungal Infections among Patients in Greece with Hematologic Disorders: The ASPIRE Study

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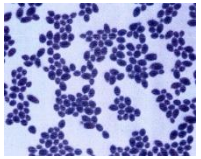
Table 3 Clinical outcome based on clinical presentation

	EORTC/MSG criteria				Total	
	No signs of IFI* (n = 74)	Possible IFI (n = 52)	Probable IFI (n = 12)	Proven IFI (n = 5)	n (%) n = 143	95% CI
Success, n (%)	67 (90.5)	50 (96.2)	9 (75.0)	5 (100)	131 (91.6)	(85.80%–95.59%)

Sonuç;

Mikafungin hematolojik maligniteli veya kök hücre nakilli hastaların **profilaksi** ve **tedavilerinde güvenle** kullanılabilir.

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU



İnvazif Kandidoz; Nötropenik hastalar

I. **2016 IDSA**

II. **2017 ECIL-6**

III. **Yeni çalışmalar**

Özet;

- ✓ Başlangıç tedavisi **ekinokandin**
  - ✓ Tür tayini sonrası etkili olan
- ✓ Metastatik komplikasyonlarda: minimum tedavi süresi eradikasyonu netleştirince ek **2 hafta**
- ✓ SVK/Port çıkarılması öneriliyor
- ✓ SVK/Port çıkartılamıyorsa **biyofilme etkili** ekinokandin veya AmfB

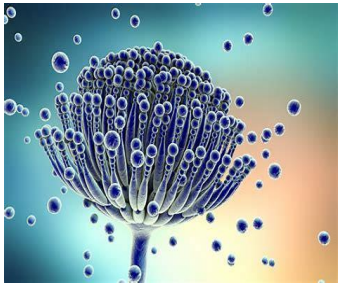
I. IDSA Management of Candidiasis. *CID.* 2016:62

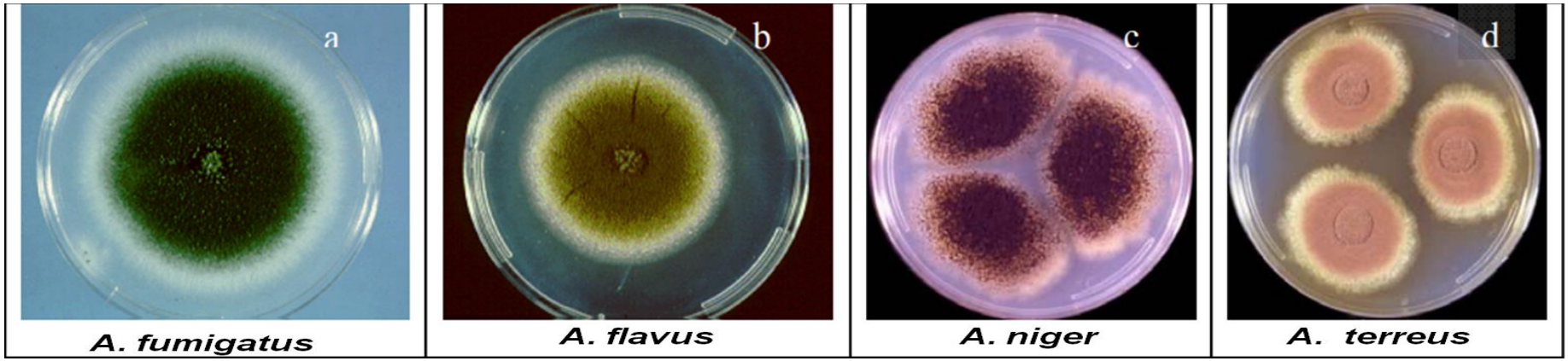
II. Tissot. F, et al. *Haematologica* 2017;102:433-44.

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Hematoloji-Onkoloji Hastalarında İFİ

- İnvazif kandidoz
- **İnvazif aspergilloz**
- İnvazif zigomikoz (mukormikoz)





MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Clinical Microbiology and Infection 24 (2018) e1–e38

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journal homepage: www.clinicalmicrobiologyandinfection.com

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

A.J. Ullmann [1, 62, 63], J.M. Aguado [2, 62, 63], S. Arikan-Akdagli [3, 62, 63], D.W. Denning [4, 5, 6, 63], A.H. Groll [7, 62, 63], K. Lagrou [8, 62, 63], C. Lass-Flörl [9, 62, 63], R.E. Lewis [10, 62], P. Munoz [11, 12, 13, 62, 63], P.E. Verweij [14, 62, 63], A. Warris [15, 62, 63], F. Ader [16, 17, 65], M. Akova [18, 62, 63], M.C. Arendrup [19, 62, 63], R.A. Barnes [20, 63], C. Beigelman-Aubry [21, 65], S. Blot [22, 23, 65], E. Bouza [11, 12, 13, 62, 63], R.J.M. Brüggemann [24, 62], D. Buchheidt [25, 62, 63],

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Tanı ve Tedavi Algoritması

Definition of patient populations:
GM (and PCR) monitoring OR mould-active prophylaxis

Symptoms (e.g. persistent fever)

Positive GM or PCR

Minimum diagnostic procedures: CT and microbiological work-up (cytology, culture & biomarkers)

CT negative / biomarker negative:
If prophylaxis: Continue prophylaxis, consider TDM, and actively exclude alternative foci (e.g. sinusitis)
If no prophylaxis: No antifungals and actively exclude alternative foci (e.g. sinusitis)

CT positive / biomarker negative:
If prophylaxis: Discontinue prophylaxis or consider TDM. Treat as recommended for targeted treatment, but change antifungal class
If no prophylaxis: Start antifungal therapy for fever-driven strategy

CT negative / biomarker positive:
Actively exclude alternative foci (e.g. sinusitis). Treat as recommended for targeted treatment, but change antifungal class if prophylaxis was given

CT positive / biomarker positive:
Treat as recommended for targeted treatment, but change antifungal class if prophylaxis was given

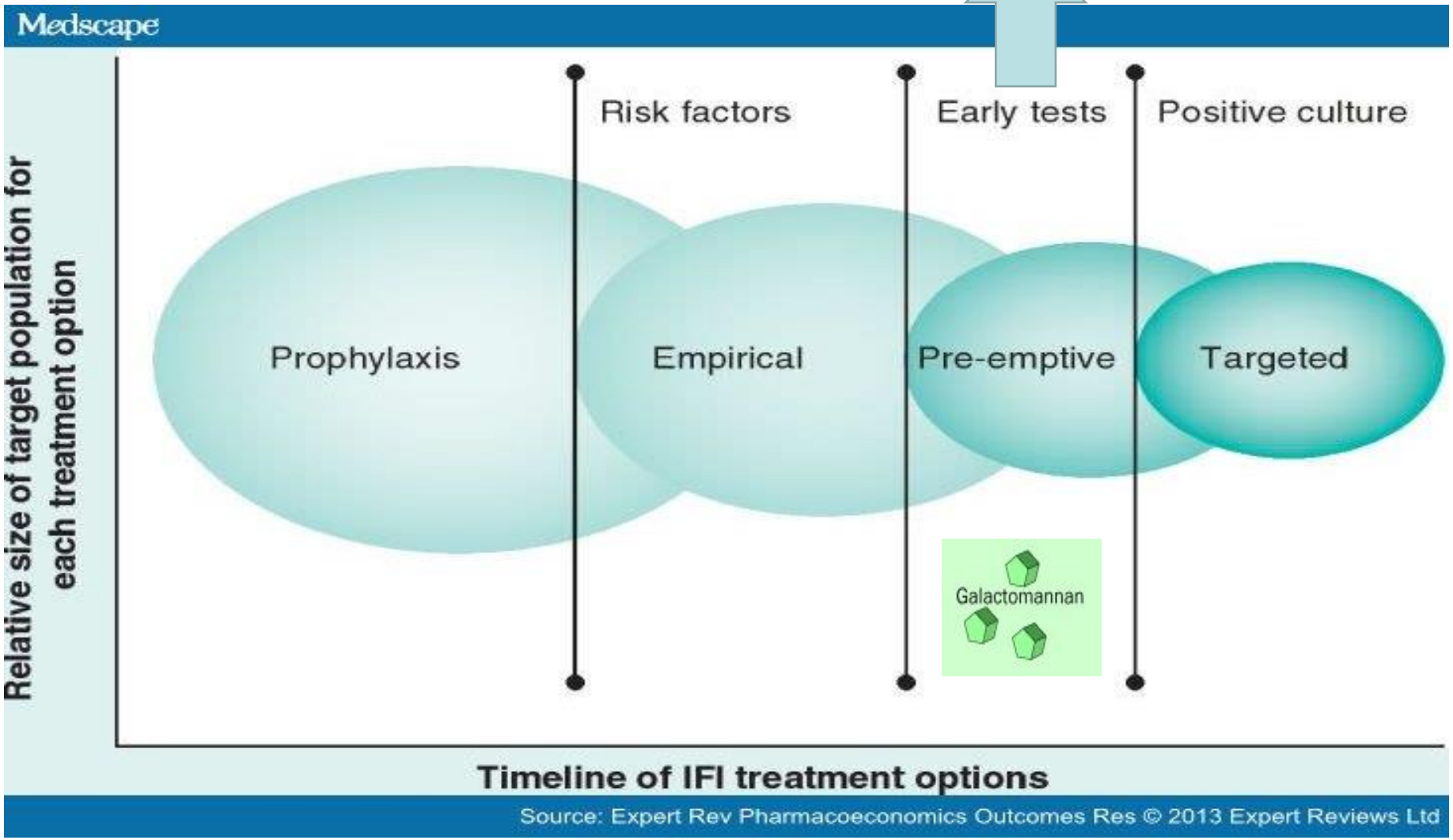
Ullmann AJ, et al. ESCMID Guide. *CMI*. 2018. e1ee38

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

“Tanı-güdümlü” tedavi

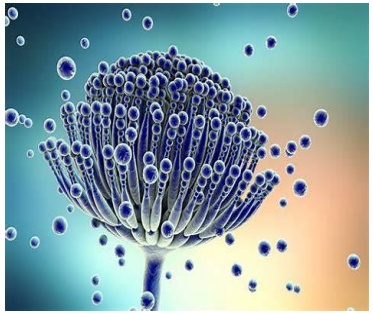
GM ve/veya beta-D-glucan

Tipik HRCT bulguları



MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İnvazif Pulmoner Aspergilloz Rehberler



I. **2016 IDSA**

II. **2017 ECIL-6**

III. **2018 ESCMID-ECMM-ERS**

IV. **2011 ATS** (~IDSA)

I. Patterson TF, et al. *CID*. 2016;63(4):e1.
II. Tissot. F, et al. *Haematologica* 2017;102:433-44.
III. Ullmann AJ, et al. *CMI*. 2018. e1ee38
VI. Limper AH,et al. *Am J Respir Crit Care Med*. 2011;183:96.

Clinical Infectious Diseases
IDSA GUIDELINE

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

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

- Tanısal inceleme devam ederken **erken antifungal tedavi**
- İlk basamak tedavide **vorikonazol (1A),**
- Kullanılamadığı durumda ve kurtarma tedavisinde **Lipo-Amfo B (2B)** veya **isavukonazol (2B)**
- Ağır hastalık ve yalnızca kurtarma tedavisinde kombinasyon: **Vorikonazol + Ekinokandinler** (2B)
- Ekinokandinler primer tedavide önerilmez.
- Süre: **6-12 hafta**

Thomas F. et al. 2016 Update by IDSA. *CID*.2016; 29: a1-60.

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

ECIL-6 : İA Başlangıç Tedavisi

Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Tissot F, et al. *Haematologica* | 2017; 102: 433-44.

Hematolojik maligniteli ve kök hücre alıcılarında İPA'da hedefe yönelik tedavi

Popülasyon	Tedavi seçeneği	ÖG/KK
1. Nötropeni (nonallo HSCT alıcıları) 2. Allo-HSCT (nötropeni) 3. Allo-HSCT (w/o nötropeni) veya diğer nötropenik olmayanlar	**İsavukonazo**l 200 mg IV tid gün 1 ve 2, sonra 200 mg qd oral	AI
	Vorikonazol 2x6 mg/kg IV (oral 400 mg bid) ilk gün, 2x4 mg/kg IV (oral 200-300 mg bid)	AI
	L-AmB 3 mg/kg	BII
	Kombine vorikonazol + anidulafungin	CI
	Kaspofungin 70 mg qd ilk gün, 50 mg qd	CII
	Itrakonazol 200 mg q12 ilk gün IV, 200 mg/qd	CIII
	AmB lipid kompleks (ABLC) 5 mg/kg	CIII
	Mikafungin 100 mg	CIII
	Konvansiyonel AmB 1-1.5 mg/kg	DI
Yaşamı tehdit eden hemoptizi (nötropeniden çıkıncaya kadar)	Arteriyel embolizasyon, acil **cerrahi** girişim	BIII

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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Başlangıç Tedavisi

❖ **Vorikonazol**

- **Vorikonazol alamayanlar:** (ciddi hepatotoksisite, ilaç etkileşimi)
  - **Lipozomal Amfo B** VEYA
  - **İsavukonazol** (renal disfonksiyon, siklodekstrin nedeniyle IV vorikonazol alamayanlar)

- Kemoterapi ilaçlarıyla **ilaç etkileşimleri**ne dikkat:
  - Etkinlik azalabilir
  - Toksisite artabilir

- Antifungal direnç: ***Aspergillus calidoustus*** , ***A. terreus, A. lentulus***, (↑ **MİK**)

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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Vorikonazol

- **Vorikonazol** (iv /:po): 1. gün: 2x6 mg/kg IV
  Sonra 2x4 mg/kg IV
  2x200 mg po, 2x4 mg/kg (**300 mg**) po

✓ **Serum kararlı düzey takibi** (5 - 7 günde 1) **>1 - < 5.5** mcg/ml

✓ **İlaç etkileşimi** (kemoterapötikler !)

Yan etkiler: görme bozukluğu
halüsinasyonlar
nöropati
QTc interval uzaması
alopesi
cilt döküntüsü , periostit

– **Nefrotoksisite**

– **CrCl <50 mL/min** olanlarda kullanılmamalı

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Amfoterisin B lipid formülasyonları

❖ **Lipozomal Amfoterisin B** (AmBisome®): 3 - 5 mg/kg/gün IV

❖ **Amfoterisin B Lipid Kompleks** (Abelcet; ABLC®) :

5 mg/kg/gün IV (kurtarma tedavisinde)

- **Vorikonazol maruziyeti + mukormikoz ihtimali** varsa…
- Tedavi empirik başlanırsa, tanısal işlemlere devam edilmeli**,**
  → **IPA tanısı kesinleşirse, vorikonazole geçilmeli**
- **Yan etkiler:** infüzyon ilişkili reaksiyonlar, elektrolit bozuklukları

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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İsavukonazol

Ön-ilaç: **İsavukonazonyum sulfat** (Cresemba®)

- **2015**: FDA ve EMA onayı
- **Yükleme dozu**: 48 saat boyunca 3 x 200 mg po veya IV
- Son yükleme dozundan 12-24 saat sonra 1 x 200 mg po veya IV

- **Yan etkiler:** bulantı, kusma, ishal, başağrısı, hipokalemi, transaminaz yüksekliği, periferal ödem, infüzyon reaksiyonları (titreme, hipotansiyon, dispne), QT interval kısalması

- Yan etkileri diğer azollerden daha az, diğer azolleri tolere edemeyenlerde kullanılabilir.

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Ekinokandinler

- **Kaspofungin (FDA onaylı) :**
  1. gün: 70 mg IV yükleme, sonrasında 50 mg IV;
  Yanıt yetersiz ise günlük doz maksimum 70 mg'a çıkartılabilir.

- **Mikafungin** (FDA onayı yok) :
  100 - 150 mg IV

- **Anidulafungin** (FDA onayı yok) :
  1. gün: 200 mg IV yükleme, sonrasında 100 mg IV.

- **Yan etkiler:** orta düzey AST- ALT- ALP yüksekliği

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Hematolojik maligniteli ve kök hücre alıcılarında akciğer dışı İA tedavisi

Popülasyon	Tedavi seçeneği	ÖG/KK
MSS İA (şüpheli veya kanıtlanmış)	Cerrahi girişim yapılmalı	AII
	Vorikonazol	AII
	Posakonazol	DIII
	Itrakonazol	DIII
	AmB lipid formülasyonları	BIII
	Konvansiyonel AmB	DI
	Ekinokandinler	DIII
İnvazif sinüs aspergillozu	Cerrahi girişim	AIII
	Lokal antifungal tedavi	CIII
	Vorikonazol	AII
	L-AmB	AII

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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Kurtarma Tedavisi

- **Tedaviye yanıtsız / ilerleyici İPA**
- Yeni bir patojen?
- Terapötik doz düzeyi, ilaç - ilaç etkileşmesi, uyum sorunu, direnç problemi ?
- **Antifungal ilaç sınıfını değiştirmeli**
- Mümkünse immünosüpresyonu azaltmalı
- Nekrotik lezyonların cerrahi rezeksiyonu
- Monoterapiye cevap yoksa **kombinasyon tedavisi**:

Vorikonazol (2B)
veya
İzavukonazol (2C)
veya
Lipozomal Amfo B (2C)

+

Kaspofungin
veya
Mikafungin
veya
Anidulafungin

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ESCMID: Azol direnci için test endikasyonları

Table 15
Indications for testing for azole resistance in clinical *Aspergillus* isolates

Population	Intention	Intervention	SoR	QoE	Comment
All clinically relevant *Aspergillus* isolates (in patient groups or regions with known azole resistance)	Identify azole resistance	Reference MIC testing	A	II	In situations where rapid testing is available
Clinically relevant *Aspergillus* isolates in patient groups with high prevalence of azole resistance or patients unresponsive to treatment	Identify isolates with intrinsic resistance	Species identification to complex level	A	III	Some species are intrinsically resistant—e.g. *A. calidoustus* (azole resistant) *and A. terreus* (AmB resistant)
Clinically relevant *A. fumigatus* isolates	Identify azole-resistant *A. fumigatus*	Routine azole agar screening	B	III	Identifies resistant colonies that require MIC-testing
All isolates –resistance surveillance	Determine the local epidemiology of azole resistance	Periodical reference MIC testing of *A. fumigatus* complex	A	II	Test at least 100 isolates
Azole-resistant isolates	Determine nature and trends in Cyp51A mutation distribution	Cyp51A-gene mutation analysis	A	II	Test resistant isolates from surveillance survey

Abbreviations: AmB, Amphotericin B; MIC, minimum inhibitory concentration; QoE, Quality of evidence; SoR, Strength of recomme

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Clinical Infectious Diseases

INVITED ARTICLE

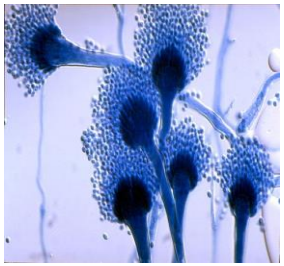
IMMUNOCOMPROMISED HOSTS: David Snydman, Section Editor

CID. 2018; 67(10):1621–30

Breakthrough Invasive Mold Infections in the Hematology Patient: Current Concepts and Future Directions

Michail S. Lionakis,[1] Russell E. Lewis,[2] and Dimitrios P. Kontoyiannis[3]

- Hematolojik maligniteli hastalarda triazol profilaksisine rağmen İFİ görülme sıklığı artmakta
- «**Breakthrough**» İFİ görülmekte (bİFİ)
- **bİFİ**→ Tedavi net değil
- **Yönetimde**; konak, lokal veriler, antifungal direnç sonuçları ve verilen profilaksi durumuna göre karar verilmeli



CT of lung[c] +/-sinus[d] ± brain[d,, #, ##]
Early bronchoscopy (within 48-72 hours)
Bronchoalveolar lavage fluid culture, galactomannan, PCR;[e]
Antifungal susceptibility testing of isolates grown from culture;[f]
Biopsy, histology and culture of suspected lesions if feasible

POS# or ISA#

TDM should be considered to document drug exposures, especially for patients on oral therapy

Risk for breakthrough with non-*Aspergillus* molds or resistant *Aspergillus* spp.

Switch to a different triazole* with similar spectrum (POS→ISA, or ISA→POS) + L- AMB (5 mg/kg/day)

VRC

TDM important to document drug exposures due to extreme PK variability

Risk for breakthrough with non-*Aspergillus* spp. (especially mucormycosis) or resistant *Aspergillus* spp.

Switch to a mold-active triazole* with broader spectrum (POS or ISA) + L-AMB (5 mg/kg/day)

Lipid AMB

Increased concern for *A. terreus*, *A. flavus* and amphotericin B-resistant non-*Aspergillus* molds (e.g., *Cunninghamella*, *Scedosporium*, *Paecilomyces*)

Mold-active triazole* (VRC, ISA) +/- Echinocandin

Echinocandin##

Breakthrough infection with all *Aspergillus* spp. and non-*Aspergillus* molds

Mold-active triazole* (VRC, ISA) +/- L-AMB (5mg/kg/day)

CID. 2018; 67:1621–30.

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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İmmuno-modülasyon

- **İmmünosüpresyonun azaltılması:**
  - Nötropenik hastalarda kemik iliği toparlanması İA kontrolü için kritik önemli
  - HSCT alıcılarında engrafman olmaması İA'a bağlı ölüme neden
- **Koloni-stimulan faktörler (CSF):** Hasta bazında risk-yarar oranı
  - Nötrofil kemotaksisi ve fagositozu arttırır.
  - G-CSF nötropeni ve hospitalizasyon süresini kısaltır.
  - İnfeksiyona bağlı mortaliteyi azalttığına dair kesin kanıt yok
- **Granülosit Transfüzyonları:** Az sayıda hasta içeren çalışma verisi mevcut

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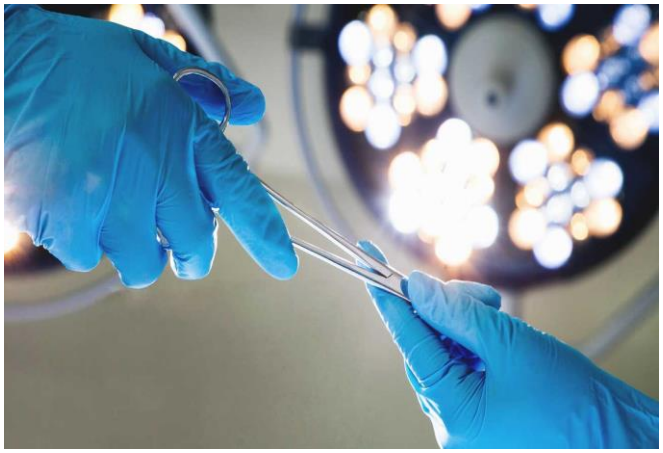
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İPA - Cerrahi

- Kronik nekrotizan hastalık varlığında nekrotik doku debridmanı
  - ✓ lezyonların yerleşimi ve yayılımı
  - ✓ gerekli rezeksiyon derecesi
  - ✓ komorbiditeler
  - ✓ cerrahiyi tolere edebilme
  - ✓ kemoterapinin gecikmesinin olası etkisi

- **Komplikasyonlar:**
  - ➢ Kanama
  - ➢ İkincil infeksiyonlar
  - ➢ İyileşmeyen yaralar



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Geliştirilmekte olan yeni anifungal ajanlar

- **CD101 (Biafungin):** haftada 1 doz, preklinik çalışmalar, korunma ve tedavide
- **E1210 (Japan):** Hücre duvarında GP1 proteinini hedefliyor, fungal büyümeyi önlüyor. Faz-I klinik çalışmalar, çoğu küf ve mayaya etkili
- **F901318 (UK):** Pirimidine biyosentezini hedefliyor. Triazol-dirençli küflere in-vitro etkili, Faz-II klinik çalışmalar
- **ASP2397 (USA):** Alüminyum demir şelasyonunu önlüyor. Faz-I klinik çalışmalar

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Maruziyetten Korunma

- Hastalar hastane içinde inşaat ve yenileme alanlarından uzak tutulmalı (AII)
- Hasta odası ve servislere saksılı bitki (BII), canlı çiçek alınmamalı (CIII)
- Mümkünse pozitif basınçlı, HEPA filtreli (BII) veya laminar akımlı (BII) odalara alınmalı
- Korunmuş alan dışında hastalar için koruyucu maskelerin etkili olmadığı kanıtlanmıştır (CII)
- Duşlarda ve su kaynaklarında filtre kullanımı önerilir (BII)
- İnfeksiyonları önlemek için düzenli ortam hava örneklemesi önerilmemekte
- Sadece filtre etkinliği için yapılabilir (BIII).

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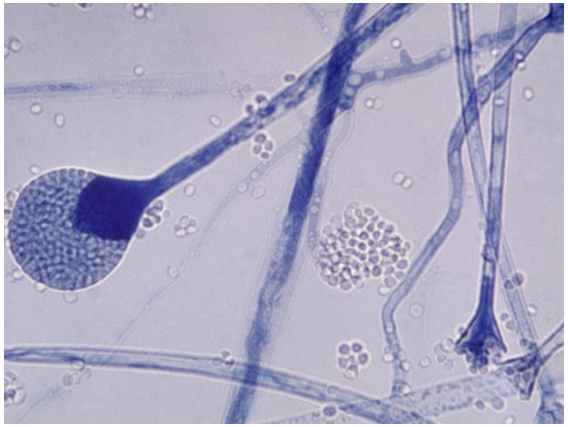
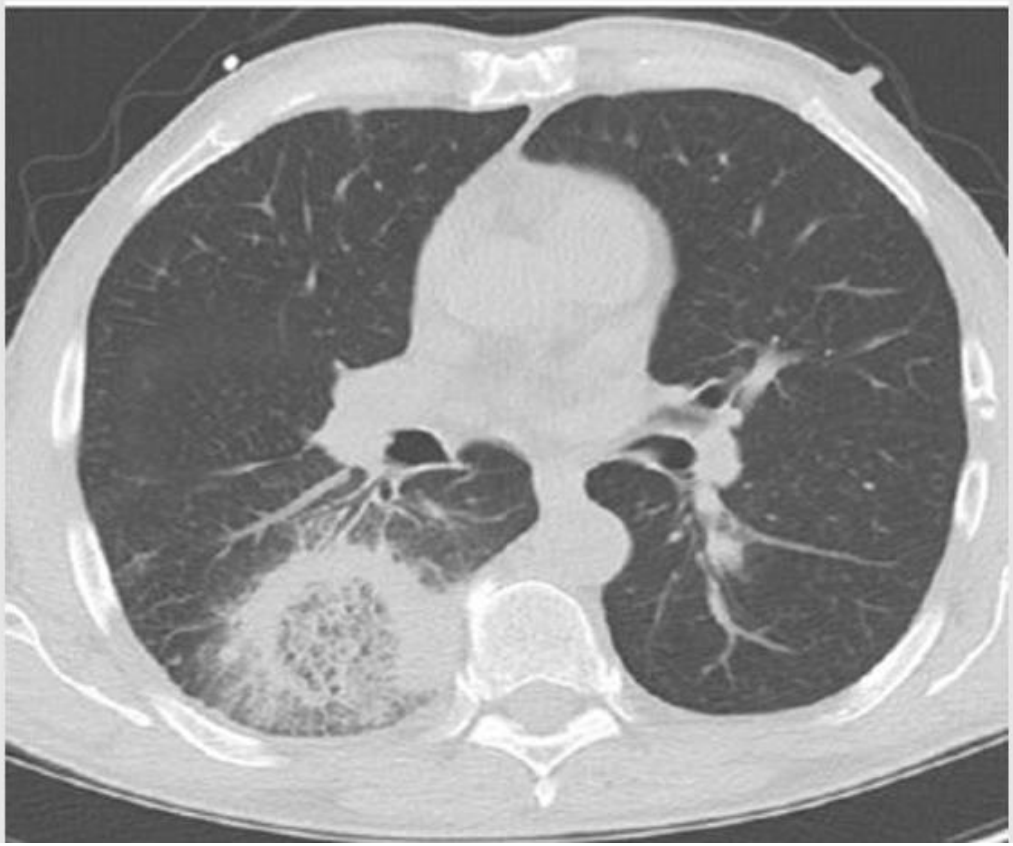
Hematoloji-Onkoloji Hastalarında İFİ

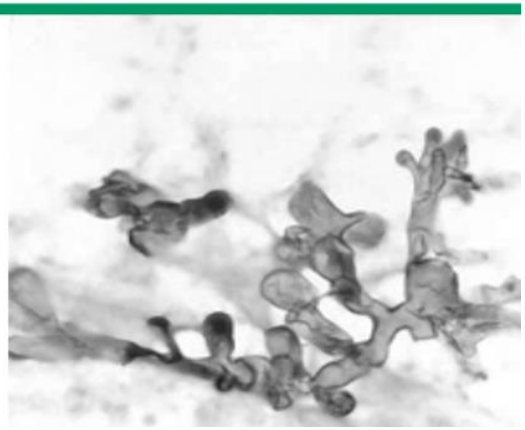
- İnvazif kandidoz
- İnvazif aspergilloz
- **İnvazif zigomikoz (mukormikoz)**



Ters halo: Mukormikoz



Mucorales hyphae



ECIL-6 : Mukormikoz Tedavisi

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

Tissot F, et al. *Haematologica* | 2017; 102: 433-44.

SUT- Antifungal

4.2.23 - Amfoterisin-B, kaspofungin, anidilofungin, vorikonazol, posakonazol (Ek:RG-09/09/2017- 30175/23-a md. Yürürlük: 23/09/2017) (oral süspansiyon ve tablet formu), **ıtrakonazol (infüzyon ve solüsyon) (Ek: RG- 18/06/2016- 29746/ 17-a md. Yürürlük: 25/06/2016)** , mikafungin **kullanım ilkeleri**

(1) **(Mülga:RG-21/03/2018- 30367/ 26-a md. Yürürlük: 01/04/2018)** ~~Hastanın böbrek ve karaciğer fonksiyonları normal ise ilk tercih klasik amfoterisin-B veya flukonazoldür.~~

(Değişik: RG- 21/03/2018- 30367/ 26-b md. Yürürlük: 01/04/2018)

~~(2) Klasik amfoterisin-B'ye alerjik reaksiyon gösterdiğinin uzman hekim raporu ile belgelenmesi ya da hastanın karaciğer veya böbrek fonksiyon testlerinin laboratuvar verileri ile bozuk olduğunun belgelenmesi halinde lipozomal veya lipid kompleks veya kolloidal dispersiyon amfoterisin-B veya kaspofungin veya anidilofungin veya posakonazol veya vorikanazol veya ıtrakonazol (infüzyon) **(Ek: RG- 18/06/2016- 29746/ 17-b md. Yürürlük: 25/06/2016)** veya mikafungin kullanılabilir.~~

(2) Bu maddede belirtilen etken maddeli ilaçların sistemik mantar enfeksiyonları tedavisinde kullanılması halinde bedelleri Kurumca karşılanır.

SUT- Antifungal

~~Mikafungin;~~

~~1) İnvaziv kandidiyazis ve özofajiyal kandidiyazis endikasyonlarında birinci ve ikinci fıkra hükümlerine göre kullanılır.~~

~~2) Allojenik hematopoietik kök hücre nakli (HSCT) yapılan hastalarda aspergilloz ve candida enfeksiyonlarının profilaksisinde yukarıda yer alan birinci ve ikinci fıkra hükümleri aranmaz.~~

~~3) 10 gün veya daha uzun süreyle nötropeni olması beklenen hastalarda Aspergilloz ve Candida enfeksiyonlarının profila ksisi endikasyonunda ödenmez.~~

(Değişik: RG- 21/03/2018- 30367/ 26-ç md. Yürürlük: 01/04/2018)

(6) Mikafungin;

1) İnvaziv kandidiyazis ve özofajiyal kandidiyazis endikasyonlarında kullanılır.

2) Allojenik hematopoietik kök hücre nakli (HSCT) yapılan hastalarda veya akut lenfositer lösemi (ALL) hastalarında nötropenik dönemde ve takip eden bir hafta içinde veya mukoziti olan otolog hematopoietik kök hücre nakli yapılan hastalarda nötropenik dönemde aspergilloz ve candida enfeksiyonlarının profilaksisinde kullanılır.

3) 10 gün veya daha uzun süreyle nötropeni olması beklenen diğer hastalarda aspergilloz ve candida enfeksiyonlarının profilaksisi endikasyonunda ödenmez.

Antifungaller ve immünosüpresiflerin klinik etkileşimleri

	Siklosporin A	Takrolimus	Mikofenolat mofetil	Sirolimus
Lipozomal AmB	Potansiyel nefrotoksisite	Potansiyel nefrotoksisite	NR	NR
Flukonazol	Siklo AUC ↑ (1.8 kat)	Oral takro kons ↑ (5 katta kadar)	NR	Sirol kons ↑
İtrakonazol	Siklo ↑	Takro ↑	NR	Sirol kons ↑
Vorikonazol	Siklo C_{max} & AUC ↑ (%13, %70)	Takro C_{max} & AUC ↑ (%117, % 221)	NR	Sirol C_{max} & AUC ↑ (6.6 kat, 11 kat)
Posakonazol	Siklo kons↑	Takro C_{max} & AUC ↑ (%121, % 358)	NR	Sirol C_{max} & AUC ↑ (6.7-kat, 8.9-kat)
Kaspofungin	Kaspofungin AUC ↑ (%35)	Takrolimus C_{min} ↓ (% 26)	–	NR
Mikafungin	–	–	–	Sirol AUC ↑ (%21)
Anidulafungin	–	–	NR	NR

Doz ayarlaması gerekmez

Kontra-indikedir

Eş zamanlı kullanılabilir , ancak monitorizasyon/doz ayarlaması gerekir

NR

KUB'de spesifik öneri yok

Hematoloji-Onkoloji Hastalarında İFİ Yönetimi

Özetle;

- İFİ'ler immünokompromize konakta hayatı tehdit eden hastalıktır
- Ampirik & tanı güdümlü yönetim gerektirir
- Lokal veriler, direnç sonuçlarının güncel takip edilmesi gerekli ve önemlidir
- Antifungal yönetim ekip işidir.

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KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

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İNFEKSİYONLARI ÇALIŞMA GRUBU

Konakta değil
doğada hayatımıza renk katsınlar

MİÇG'ye bekliyoruz…