İnvaziv küfler

Dr. Duygu Mert

Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği

TÜRKİYE EKMUD ANKARA GÜNLERİ

8 Kasım 2023

Case Reports > Hematol Rep. 2017 Jun 1;9(2):6997. doi: 10.4081/hr.2017.6997.

Invasive Aspergillosis with Disseminated Skin Involvement in a Patient with Acute Myeloid Leukemia: A Rare Case

Duygu Mert [1], Gülşen Iskender [1], Fazilet Duygu [1], Alparslan Merdin [2], Sinan Dal Mehmet [1], Mehmet Dogan [3], Emre Tekgündüz [2], Mustafa Ertek [1], Fevzi Altuntaş [2]

Affiliations + expand

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Free PMC article

Hematology Reports 2017; volume 9:6997

Invasive aspergillosis with disseminated skin ınvolvement in a patient with acute myeloid leukemia: a rare case

Duygu Mert,[1] Gülşen Iskender,[1] Fazilet Duygu,[1] Alparslan Merdin,[2] Mehmet Sinan Dal,[1] Mehmet Dogan,[3] Emre Tekgündüz,[2] Mustafa Ertek,[1] Fevzi Altuntaş[2]

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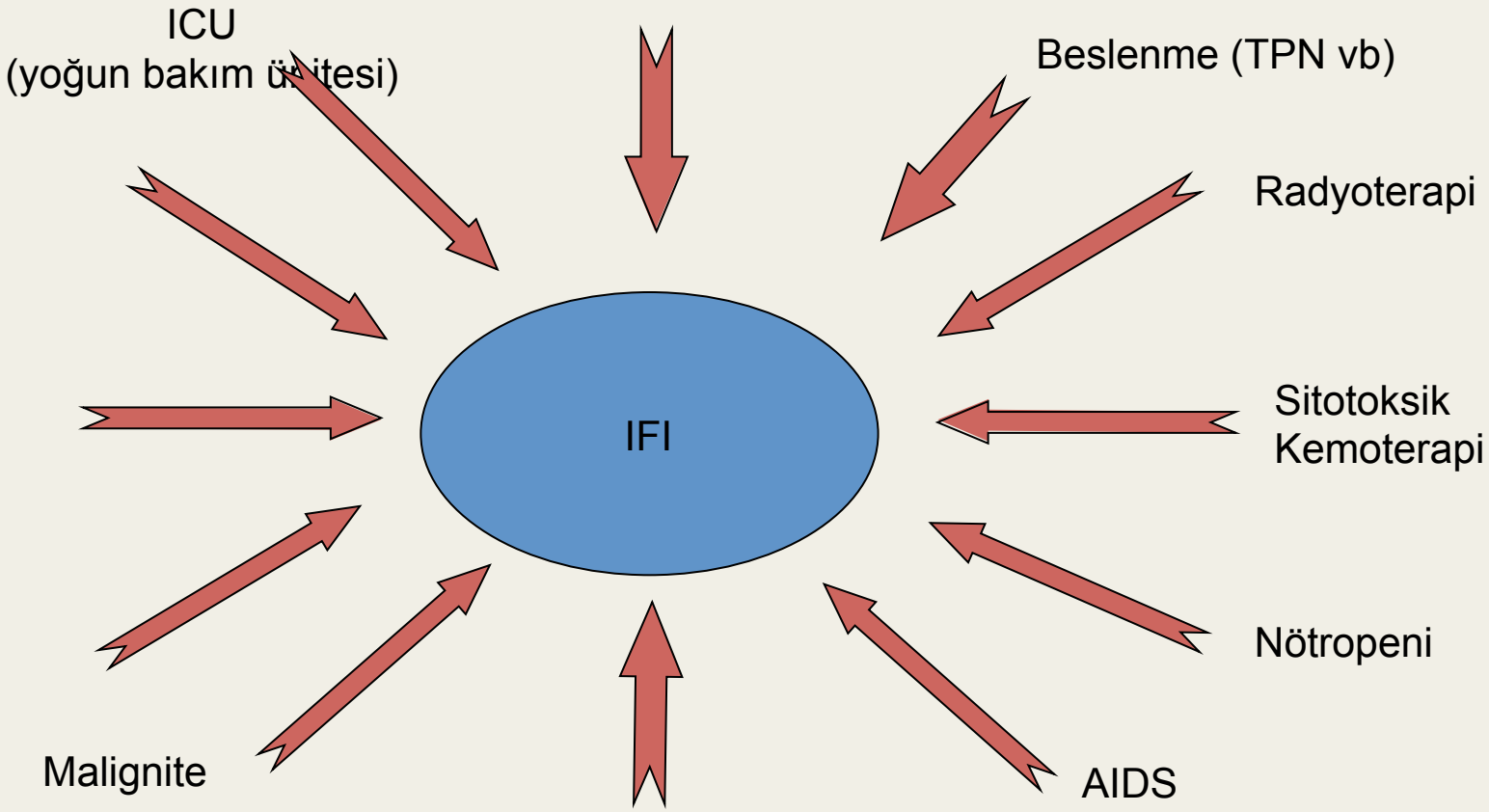
Tartışma
İnvaziv aspergilloz

- *Aspergillus* doğada bulunan bir küftür.
- Akciğer dışındaki dokularda da enfeksiyona neden olabilir.
- Bağışıklık sistemi baskılanmış hastalarda, özellikle uzun süre nötropenik olanlarda görülür.

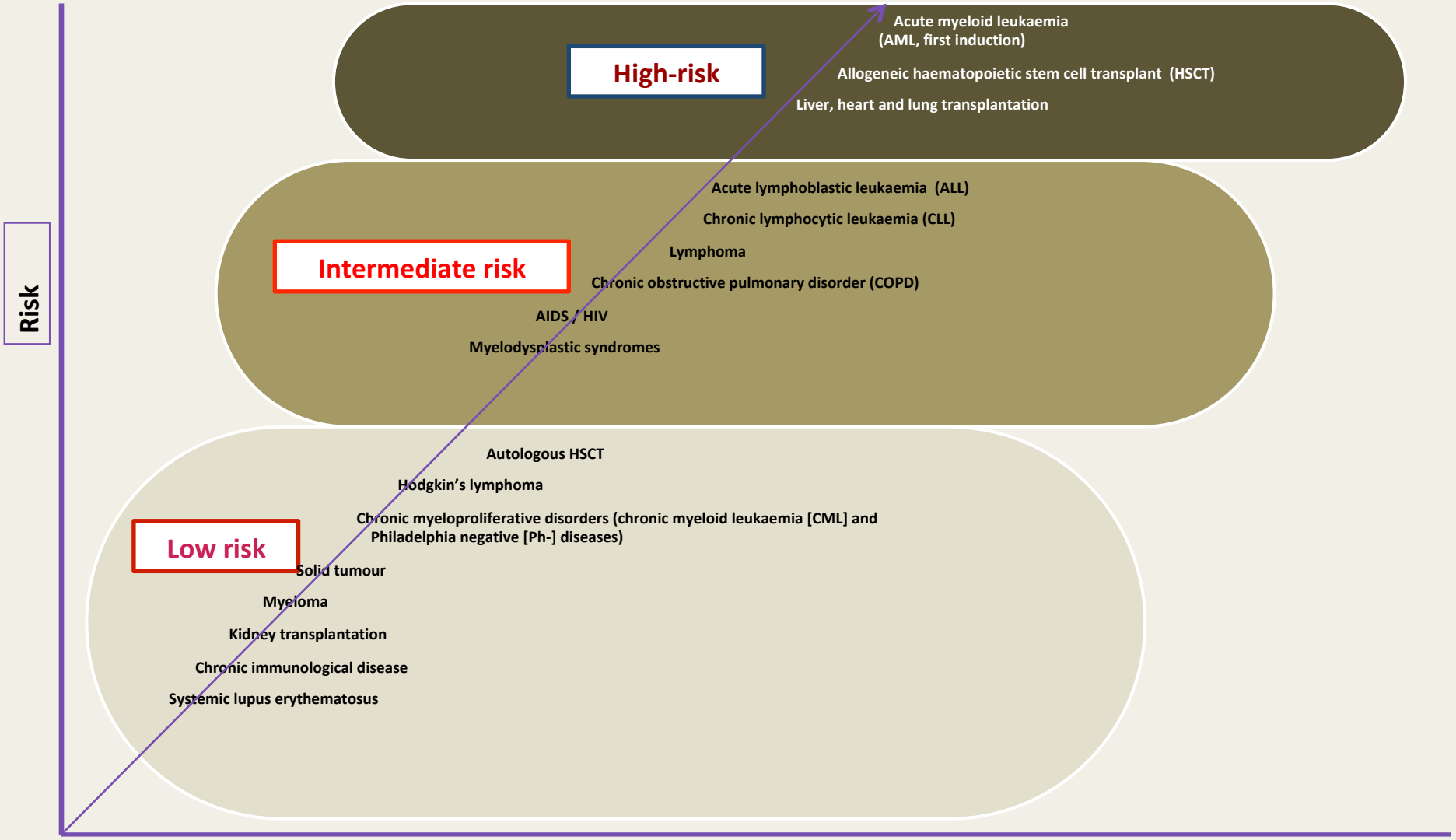
- Schwartz S, Thiel E. Clinical presentation of invasive aspergillosis. Mycoses 1997;40:S21-4.
- Walsh TJ. Invasive pulmonary aspergillosis in patients with neoplastic diseases. Semin Respir Infect 1990;5:111-2

IFI'nin gelişmesine zemin hazırlayan başlıca faktörler



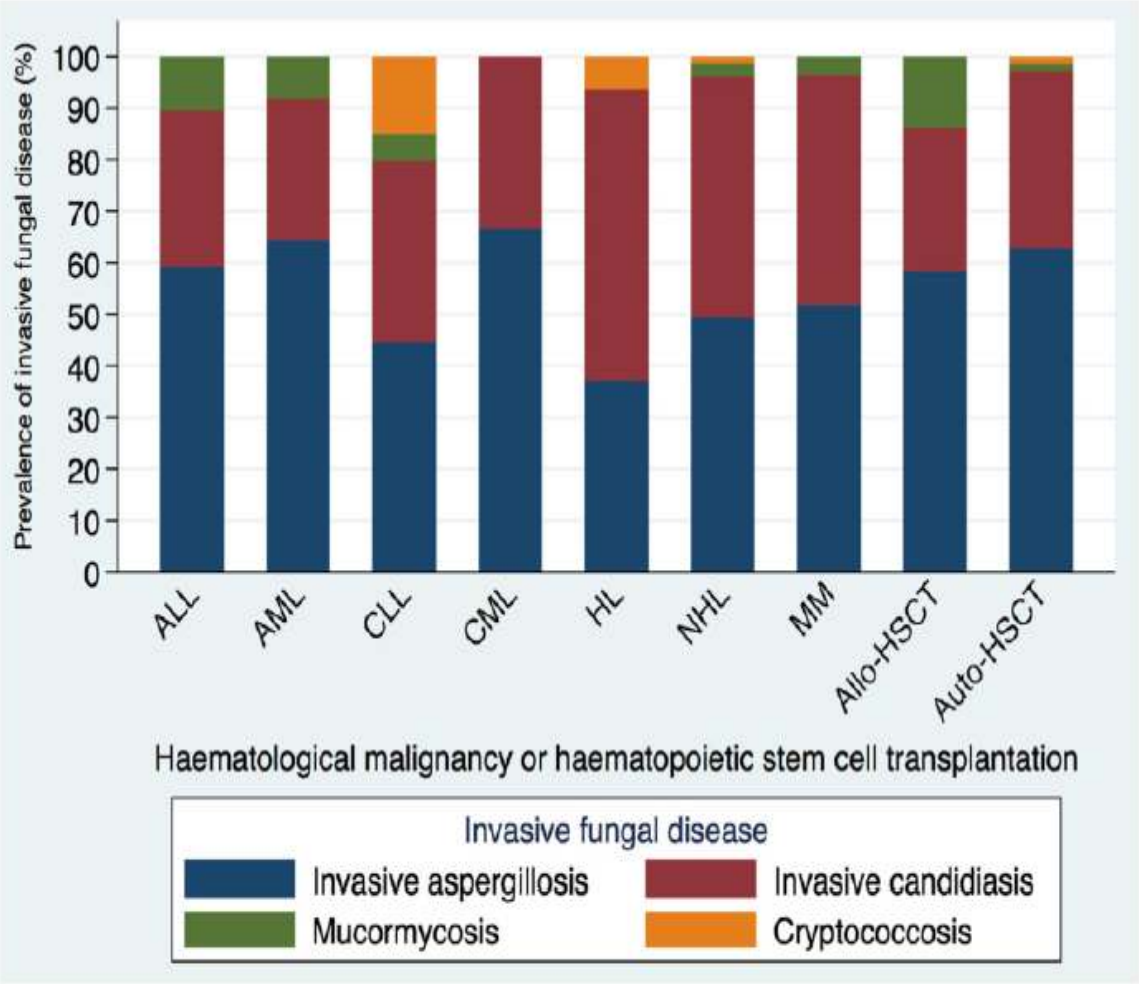
Muhlemann K, *Leukemia* 2005;19:545–550.
Sole A, ve ark. *Clin Microbiol Infect.* 2005;11(5):359-65.
Singh N ve ark. *Clin Microbiol Rev*. 2005;18(1):44-69.
Thursky K ve ark. *Bone Marrow Transplant*. 2004;34(2):115-21

İmmunkomprimize hastalarda altta yatan duruma göre risk değerlendirmesi



Pagano L, et al. *J Antimicrob Chemother* 2011; 66 Suppl 1: i5–14.

Hematolojik malignitelerde fungal enfeksiyonların sıklığı



Valentineet al. ; BMC Infectious Diseases(2019) 19:274

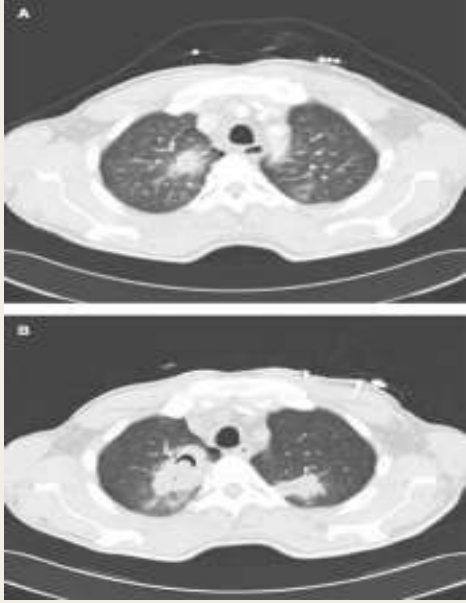
Tartışma
İnvaziv aspergilloz

- Bağışıklık sistemi baskılanmış hastalarda önemli bir morbidite ve mortalite nedenidir.

- Erken tanı ve tedaviye rağmen ölümcül olabilir.

- Schwartz S, Thiel E. Clinical presentation of invasive aspergillosis. Mycoses 1997;40:S21-4.
- Walsh TJ. Invasive pulmonary aspergillosis in patients with neoplastic diseases. Semin Respir Infect 1990;5:111-

Tartışma
İnvaziv aspergilloz



- Tanı, dokuda mantarların gösterilmesi ve kültürde üreme ile konur.

- Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001;32:358-66.
- Van Burik JA, Colven R, Spach DH. Cutaneous aspergillosis. J Clin Microbiol 1998;36:3115.

Tartışma
İnvaziv aspergilloz

- *Aspergillus*'un konilerinden salınan sporlar çevrede bulunur.

- Kutanöz aspergilloz travma varlığında direkt inokülasyon, sekonder komşuluk veya kan yoluyla yayılır.

Tartışma
İnvaziv aspergilloz

- Tanıda galaktomannan ve beta-D-glukan testleri kullanılır.

- BAL ve/veya balgam örnekleri de analiz edilebilir.

Tartışma
İnvaziv aspergilloz

- BAL sıvısı elde edilirse galaktomannan antijen testi yapılmalıdır.

- Galaktomannan antijeni *Aspergillus*'un hücre duvarında bulunan bir polisakkarittir.

- Shannon VR, Andersson BS, Lei X, et al. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. Bone Marrow Transplant 2010;45:647.
- Sampsonas F, Kontoyiannis DP, Dickey BF, Evans SE. Performance of a standardized bronchoalveolar lavage protocol in a comprehensive cancer center: a prospective 2-year study. Cancer 2011;117:3424.

Tartışma
İnvaziv aspergilloz

- Galaktomannan antijeni serumda ve/veya BAL sıvısında tespit edilebilir.

- Olguda, BAL sıvısında galaktomannan antijeni pozitif bulunmuştur.

- Tanıda görüntüleme de önemlidir.

Tartışma
İnvaziv aspergilloz

- Toraks BT tanıda faydalıdır.

- İnvaziv pulmoner aspergillozla ilişkili görüntüleme bulguları diğer anjiyoinvaziv akciğer enfeksiyonlarında da görülmektedir.

Tartışma
İnvaziv aspergilloz

- Şüphelenilen vakalarda;

➢ Serum galaktomannan testi,

➢ BT taraması da dahil kapsamlı bir inceleme yapılmalıdır.

- Agrawal S, Hope W, Sinkó J, Kibbler C. Optimizing management of invasive mould diseases. J Antimicrob Chemother 2011;66:i45-53.

Tartışma
İnvaziv aspergilloz

- Bir çalışmada 1410 olguda invaziv aspergillozun kutanöz tutulum oranının en az %1 olduğu bildirilmiştir.

- Başka bir çalışmada da kutanöz tutulum oranının %4 olduğu belirtilmiştir.

- Bernardeschi C, Foulet F, Ingen-Housz-Oro S, et al. Cutaneous ınvasive aspergillosis: retrospective multicenter study of the french ınvasive-aspergillosis registry and literature review. Medicine (Baltimore) 2015;94:e1018.
- D'Antonio D, Pagano L, Girmenia C, et al. Cutaneous aspergillosis in patients with haematological malignancies. Eur J Clin Microbiol Infect 2000;19:362-5

Tartışma
İnvaziv aspergilloz

- Tedavide primer ilaç olarak **vorikonazol** önerilmektedir.

- Olguda vorikonazol başlandıktan sonra lezyonlar gerilemiş ve ciltte yeni lezyonlar oluşmamıştır.

- Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidlines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327-60.

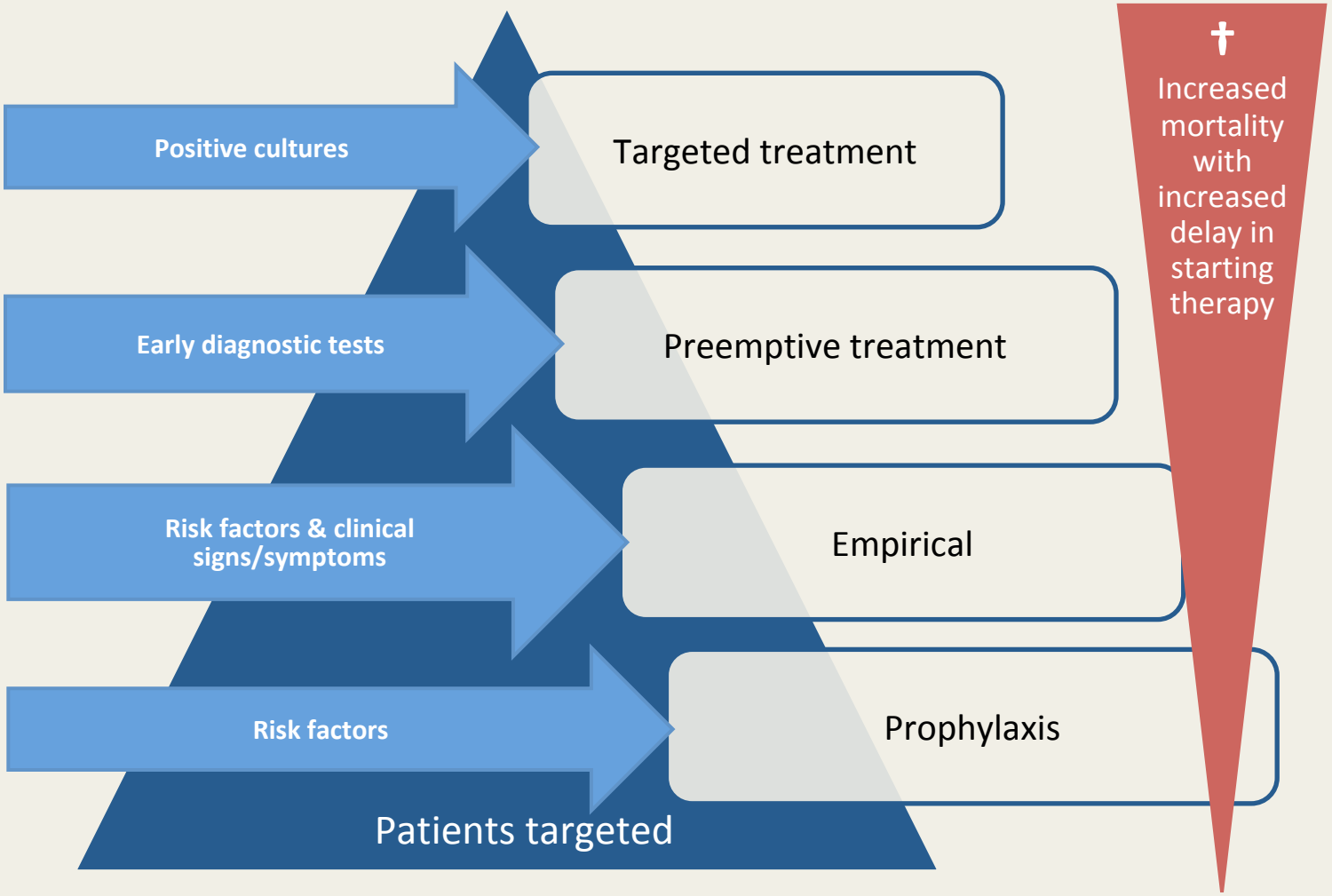
Sonuç
İnvaziv aspergilloz

- Kemoterapi alan lösemi hastalarında gelişen deri lezyonlarının histopatolojik ve mikrobiyolojik olarak değerlendirilmesi gerekir.

- Bu tür lezyonlarda mantar enfeksiyonu da akla gelmelidir.

- Mantar enfeksiyonlarında deri tutulumu araştırılmalıdır.

Different antifungal strategies for treatment of invasive fungal infections (IFIs) based on diagnostic stage



Adapted from Zaragoza et al. 2008.

Zaragoza R, et al. *Ther Clin Risk Manag* 2008; 4: 1261–80.

EORTC (Avrupa Kanser Araştırma ve Tedavi Organizasyonu)

ve

MSGERC (Mikoz Çalışma ve Araştırma Grubu-ABD tarafı) 2020 yılında güncellendi.

Kanıtlı (Proven) IFI Kriterleri
2020 EORTC/MSGERC

Mantar	Mikroskobik analiz steril	Kültür : steril	Kan örneği	Seroloji	Doku nükleik asit tanısı
Küfler	İğne aspirasyonu veya bx le elde edilen bir numunenin histopatolojik, sitopatolojik veya doğrudan mikroskobik incelemesi hif veya melanize maya benzeri formların ilişkili doku hasarının kanıtlarıyla birlikte görülmesi	steril ; klinik olarak veya radyolojik olarak anormal bir bölgeden steril bir prosedürle elde edilen bir numunenin kültürü sonucu hiyalin veya pigmentli bir küfün üretilmesi	Fusarium türleri gibi küflerin kanda üretilmesi ** aspergillus üremesi çoğunlukla kontaminasyon kabul edilir, nadiren endovasküler hastalığı gösterir.	Uygulanmaz	Formalinle sabitlenmiş parafine gömülü dokuda küfler görüldüğünde PCR ile mantar DNA'sının amplifikasyonu
Maya	Maya hücrelerini gösteren steril bir bölgeden iğne aspirasyonu veya bx ile elde edilen bir örneğin histopatolojikveya doğrudan mikroskobik incelemesiyle kapsüllenmiş tomurcuklanan mayaları gösteren Cryptococcus türleri veya psödohifleri veya gerçek hifleri gösteren Candida türlerinin görülmesi	Klinik ile tutarlı , steril bir bölgeden steril bir prosedürle (yeni yerleştirilmiş [<24 saat önce] dren dahil) elde edilen bir numunenin kültürü ile mayanın üretilmesi	Maya (ör. Cryptococcus veya Candida türleri) veya maya benzeri mantarlar (ör. Trichosporon türleri) üretilmesi	Beyin omurilik sıvısı veya kandaki kriptokokal antijen Cryptococcusu doğrular.	Formalinle sabitlenmiş parafine gömülü dokuda mayalar görüldüğünde DNA dizilemesi ile birlikte PCR ile mantar DNA'sının amplifikasyonu
Pnömosistis	Dokuda, BAL sıvısında, balgamdakonvansiyonel veya immünofloresan boyamayla mikroskobik olarak tespiti	Uygulanmaz	Uygulanmaz	Uygulanmaz	Uygulanmaz
Endemik Mikozlar	Etkilenen bir bölgeden alınan örneklerin histopatolojisi veya doğrudan mikroskopisi ile mantarın tanımlanması	Etkilenen bölgeden alınan örneklerden mantar kültürü	Kan kültüründe mantar üremesi	Uygulanmaz	Uygulanmaz

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]

[1]University of Texas Health Science Center at San Antonio and South Texas Veterans Health Care System; [2]University of California, Davis; [3]National Aspergillosis Centre, University Hospital of South Manchester, University of Manchester, United Kingdom; [4]Massachusetts General Hospital and Harvard Medical School, and [5]Tufts Medical Center, Boston, Massachusetts; [6]University of Strasbourg, France; [7]University of Texas MD Anderson Cancer Center, Houston; [8]Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; [9]Hennepin County Medical Center and University of Minnesota, Minneapolis; [10]University of Pittsburgh, Pennsylvania; [11]University at Buffalo Jacobs School of Medicine and Biomedical Sciences, and Roswell Park Cancer Institute, New York; [12]Duke University Medical Center, Durham, North Carolina; [13]California Institute for Medical Research, San Jose; [14]New York–Presbyterian Hospital/Weill Cornell Medical Center, New York; [15]University of Florida, Gainesville; [16]University of Minnesota, Minneapolis; [17]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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

Table 1. Summary of Recommendations for the Treatment of Aspergillosis

Condition	Therapy: Primary	Therapy: Alternative	Comments
Invasive syndromes of *Aspergillus*			
IPA	Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)	Primary combination therapy is not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; dosage in pediatric patients for voriconazole and for caspofungin is different than that of adults; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined
Invasive sinus aspergillosis	Similar to IPA	Similar to IPA	Surgical debridement as an adjunct to medical therapy
Tracheobronchial aspergillosis	Similar to IPA	Adjunctive inhaled AmB may be useful	Similar to IPA
Aspergillosis of the CNS	Similar to IPA	Similar to IPA Surgical resection may be beneficial in selected cases	This infection is associated with the highest mortality among all of the different patterns of IA; drug interactions with anticonvulsant therapy
Aspergillus infections of the heart (endocarditis, pericarditis, and myocarditis)	Similar to IPA	Similar to IPA	Endocardial lesions caused by *Aspergillus* species require surgical resection; *Aspergillus* pericarditis usually requires pericardiectomy
Aspergillus osteomyelitis and septic arthritis	Similar to IPA	Similar to IPA	Surgical resection of devitalized bone and cartilage is important for curative intent
Aspergillus infections of the eye (endophthalmitis and keratitis)	Systemic IV or oral voriconazole plus intravitreal AmB or voriconazole indicated with partial vitrectomy	Similar to invasive pulmonary aspergillosis; limited data with echinocandins and poor ocular penetration by this class	Systemic therapy may be beneficial in management of *Aspergillus* endophthalmitis; ophthalmologic intervention and management is recommended for all forms of ocular infection; topical therapy for keratitis is indicated

Clinical Infectious Diseases

IDSA GUIDELINE

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

Cutaneous aspergillosis	Similar to IPA	Similar to IPA	Surgical resection is indicated where feasible
Aspergillus peritonitis	Similar to IPA	Similar to IPA	Removal of peritoneal dialysis catheter is essential
Empiric and preemptive antifungal therapy	For empiric antifungal therapy, Liposomal AmB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (100 mg day), voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or 3–4 mg/kg q 12 h)		Preemptive therapy is a logical extension of empiric antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (eg, pulmonary infiltrate or positive GM assay result)
Prophylaxis against IA	Posaconazole: Oral suspension: 200 mg TID Tablet: 300 mg BID on day 1, then 300 mg daily IV: 300 mg BID on day 1, then 300 mg daily	Voriconazole (200 mg PO BID), itraconazole suspension (200 mg PO every 12 h); micafungin (50–100 mg/day), caspofungin (50 mg/day)	Efficacy of posaconazole prophylaxis demonstrated in high-risk patients (patients with GVHD and neutropenic patients with AML or MDS)
Saprophytic or colonizing syndromes of *Aspergillus*			
Aspergilloma	No therapy or surgical resection	Itraconazole or voriconazole; similar to IPA	The role of medical therapy in the treatment of aspergilloma is uncertain; penetration into preexisting cavities may be minimal for AmB
Chronic cavitary pulmonary aspergillosis	Similar to IPA	Similar to IPA	Innate immune defects demonstrated in most of these patients; long-term therapy may be needed; surgical resection may lead to significant complications; anecdotal response to IFN-γ. Tranexamic acid may be helpful in management of hemoptysis
Allergic syndromes of *Aspergillosis*			
ABPA	Itraconazole	Oral voriconazole (200 mg PO every 12 h) or posaconazole (dosage depends on formulation)	Corticosteroids are a cornerstone of therapy for exacerbations; itraconazole has a demonstrable corticosteroid-sparing effect
Allergic rhinosinusitis caused by *Aspergillus*	Polypectomy and sinus washout with intranasal corticosteroids	Antifungal therapy reserved for refractory or relapsing cases	

Abbreviations: ABLC, amphotericin B lipid complex; ABPA, allergic bronchopulmonary aspergillosis; AmB, amphotericin B; AML, acute myelogenous leukemia; BID twice daily; CNS, central nervous system; GM, galactomannan; GVHD, graft-vs-host disease; IA, invasive aspergillosis; IFN-γ, interferon gamma; IPA, invasive pulmonary aspergillosis; IV, intravenous; MDS, myelodysplastic syndrome; PO, oral; TID, 3 times daily.

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

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Haematologica 2017
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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]

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.

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]

Table 8. ECIL-6 recommendations for salvage therapy of invasive aspergillosis.

	Grade	Comments
Liposomal amphotericin B	B II	No data on voriconazole failure
Amphotericin B lipid complex	B II	No data on voriconazole failure
Caspofungin	B II	No data on voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole[a]	B II	No data on voriconazole failure
Voriconazole[a]	B II	If not used in first-line
Combination	B II	Various studies and conflicting results

[a]Monitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

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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], J. Cadranel [26, 65], E. Castagnola [27, 62], A. Chakrabarti [28, 63], M. Cuenca-Estrella [29, 62, 63], G. Dimopoulos [30, 65], J. Fortun [31, 62, 63], J.-P. Gangneux [32, 62, 63], J. Garbino [33, 62, 63], W.J. Heinz [1, 62, 63], R. Herbrecht [34, 62], C.P. Heussel [35, 63], C.C. Kibbler [36, 63], N. Klimko [37, 63], B.J. Kullberg [24, 62, 63], C. Lange [38, 39, 40, 65], T. Lehrnbecher [41, 63], J. Löffler [1, 62, 63], O. Lortholary [42, 62, 63], J. Maertens [43, 62, 63], O. Marchetti [44, 45, 62, 63], J.F. Meis [46, 62, 63], L. Pagano [47, 63], P. Ribaud [48], M. Richardson [4, 5, 6, 62, 63], E. Roilides [49, 50, 62, 63], M. Ruhnke [51, 62, 63], M. Sanguinetti [52, 62, 63], D.C. Sheppard [53, 62, 63], J. Sinkó [54, 62], A. Skiada [55, 62, 63], M.J.G.T. Vehreschild [56, 57, 58, 63], C. Viscoli [59, 62, 63],

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Table 2
Recommendations for imaging and bronchoalveolar lavage

Population	Intention	Intervention[a]	SoR	QoE	Comment	Ref.
Neutropenia, fever or clinical symptoms of pneumonia, empiric antibiotics failing to achieve defervescence, e.g. FUO	To detect pulmonary infiltrates	Chest CT and thin section multi-detector CT (MDCT)	A	II	Dose optimization recommended	[21,31,35,366]
	To identify vessel occlusion	Chest angio-CT/pulmonary CT angiography	B	II		[24–26]
Haemoptysis	To identify vessel erosion	Chest angio-CT/pulmonary CT angiography	A	II		[367,368]
Any, with infiltrate	To identify possible underlying fungal or other infectious disease	BAL	A	II		[21,49–54]
Any, with infiltrate	To obtain appropriate specimens for microscopy, culture and PCR	CT-guided BAL	A	III		[55,56]

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; FUO, fever of unknown origin; PCR, polymerase chain reaction; QoE, Quality of evidence; SoR, Strength of recommendation.

[a] Diagnostic tests are interventions.

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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

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Table 27
Targeted therapy of pulmonary disease—first line

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment	Ref.
1] Neutropenia (non-allo HSCT recipients) 2] Allo-HSCT (during neutropenia) 3] Allo-HSCT (w/o neutropenia) or other non-neutropenic patients	To increase response and survival rate	Isavuconazole 200 mg IV tid day 1–2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis fewer adverse effects than voriconazole	[173,507,564,565]
		Voriconazole 2× 6 mg/kg IV (oral 400 mg bid) on day 1, then 2–4 mg/kg IV (oral 200–300 mg bid)	A	I	II_t	II_t	C III for start with oral; D III, if prior mould active azole prophylaxis; TDM	[170,172,507,566]
		L-AmB 3 mg/kg	B	II	II_t	II_t		[171]
		Combination of voriconazole 6/4 mg/kg bid (after 1 week oral possible (300 mg bid)) + anidulafungin 200/100 mg	C	I	II_t	II_t	No significant difference compared to voriconazole, in GM-positive (subgroup) better survival; TDM	[172,566]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	C	II	II	II		[567–569]
		Itraconazole 200 mg q12 h IV on day 1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis	[507,537]
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III		[570]
		Micafungin 100 mg	C	III	III	III		[571–573]
		AmB colloidal dispersion (ABCD) 4–6 mg/kg	D	I	II_t	II_t		[142]
		Conventional AmB 1–1.5 mg/kg	D	I	II_t	II_t		[170]
		Other combinations	D	III	III	III	Efficacy unproven	[574]
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III		[575]

Abbreviations: allo-HSCT, allogeneic haematopoietic stem cell transplantation; AmB, amphotericin B; bid, twice daily; GM, galactomannan; IA, invasive aspergillosis; IV, intravenous; qd, once daily; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring; tid, thrice daily.

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Table 28
Targeted therapy of extrapulmonary disease—first line

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Suspected or proven IA of the central nervous system	To increase response and survival rate	Surgical debridement, if surgically possible	A	II_u		[576,577]
		Voriconazole	A	II_u	$n = 5/5$	[170]
					$n = 81$, 48 proven cases, 33 probable cases, TDM recommended targeting trough concentration of 2–5.5 mg/L	[576]
		Posaconazole	D	III	8 patients documented in studies (5 failures)	[578]
		Itraconazole	D	III		
		Lipid formulations of AmB	B	III	Case collections, animal data	[579–581]
		cAmB	D	I	Renal toxicity	[189,582–584]
		Echinocandins	D	III	Insufficient tissue penetration	[580]
Patients with clinical suspicion of or proven invasive sinus aspergillosis	To cure	Surgery	A	III	Need to be considered on an individual basis and decision	
Patients with invasive sinus aspergillosis (all levels of certainty: suspected through proven)		Local antifungal therapy	C	III		
		Voriconazole	A	II_t	$n = 8/7$, TDM recommended	[170,585]
		L-AmB	A	II_t	Active against mucormycosis as well since mixed infections occur or cannot be differentiated	[171]
		Posaconazole, itraconazole, echinocandins	C	III	Not well specified in studies, TDM recommended for posaconazole and itraconazole	[586,587]

Abbreviations: AmB, Amphotericin B, cAmB, conventional amphotericin B; L-AmB, liposomal amphotericin B; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring.

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Table 32
Treatment in non-haematological patients

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
HIV	To treat IA	Voriconazole	A	III	Consider drug–drug interactions with antiretroviral drugs.	[620]
SOT Heart	To treat IA	Itraconazole	C	III	6 patients cured with itraconazole 200–400 mg/day Erratic absorption and interaction with calcineurin inhibitors and other agents	[621]
SOT, any	To treat IA	Voriconazole	A	III	e.g. Herbrecht study 11 SOT; voriconazole increases the levels of anti-calcineurin immunesuppressors, TDM; monitor liver function tests especially in liver transplant recipients.	[170,214,287,333, 600,622–624,625–627]
OT, any	To treat IA	L-AmB	A	II		[628–630]
SOT, any	To treat IA	Voriconazole & caspofungin	B	II	40 SOT voriconazole & caspofungin ($n = 40$) vs amphotericin B ($n = 47$). Survival benefit in patients with *A. fumigatus* or renal insufficiency	[289]
SOT, if voriconazole contraindicated	To treat IA	Caspofungin	B	III	Complete response 83%; response 7/9 monotherapy and 7/10 combination	[631–634]

Abbreviations: HIV, human immunodeficiency virus; IA, invasive aspergillosis; L-AmB, Liposomal amphotericin B; QoE, Quality of evidence; SoR, Strength of recommendation; SOT, solid organ transplantation; TDM, therapeutic drug monitoring.

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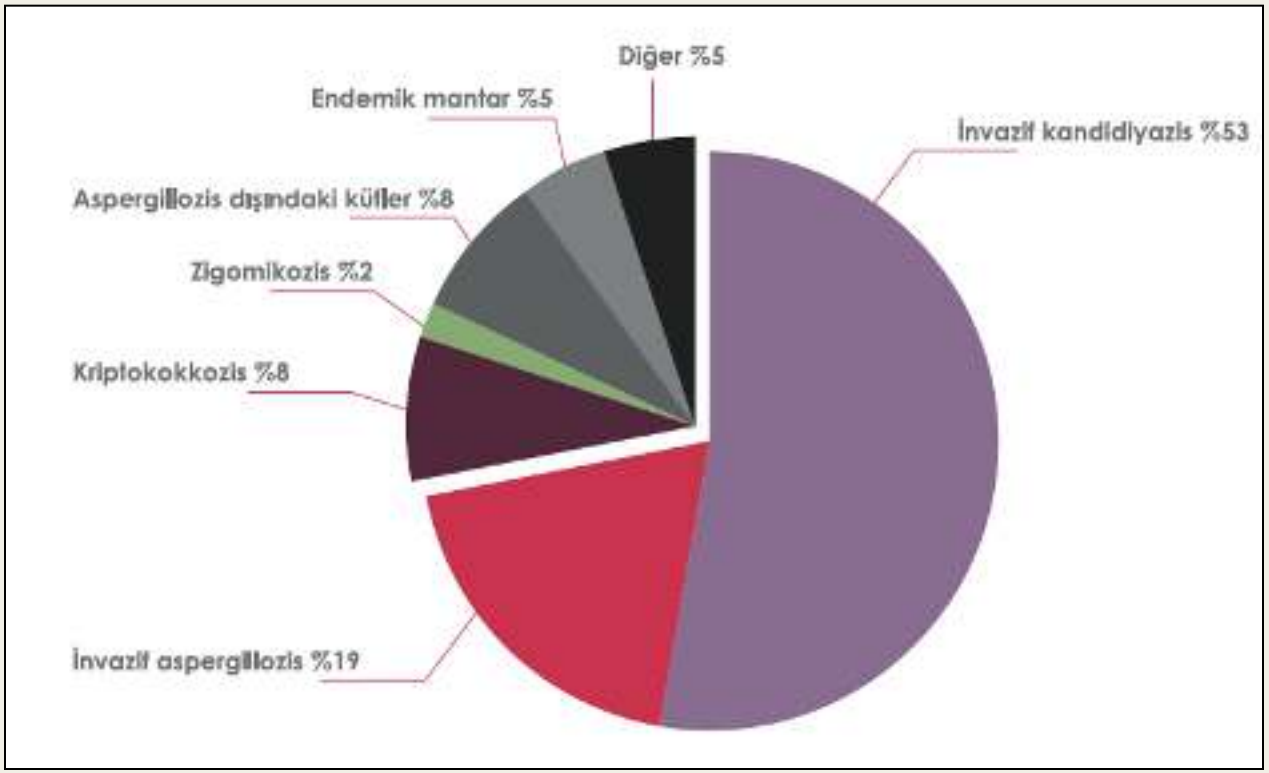
Table 37
Antifungal drugs in refractory disease

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Haematological patients with refractory IA	Achieve complete or partial response, or stable disease, improve survival	Switch to another drug class	A	III		
		Any combination	C	III	No prospective study demonstrated superiority of combination therapy over monotherapy	[715]
		Voriconazole	A	II		[333,716,624,717]
		L-AmB 3–5 mg/kg	B	II	Majority voted for BII others for AII	[676,718,719]
		ABLC 5 mg/kg	C	II		[570,719,720,628]
		ABCD			No longer commercially available	[721,722]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	B	II	Very few data in case of voriconazole/ posaconazole failure	[335,717,723–727,633,728]
		Micafungin 75–200 mg qd	C	II		[572,729]
		Posaconazole 200 mg qid or 400 mg bid suspension or 300 mg tablet bid day 1, followed by 300 mg qd	B	II		[138,336,730,731]
		Itraconazole	D	III	In case of refractoriness to voriconazole	
		Itraconazole oral forms	C	II	Poor bioavailability	[126]
		Itraconazole IV formulation			Commercially not available everywhere	[537,732]

Abbreviations: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; bid, twice daily; IV, intravenous; L-AmB, Liposomal amphotericin B;; qd, once daily; qid, four times daily; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring.

Fungal enfeksiyonlara en sık yol açan patojenler kandida ve aspergillus türleridir.[1]



Günümüzde fungal enfeksiyonların %28'ine *Aspergillus* ya da *Candida* türleri dışındaki patojenler neden olmaktadır.[1]

ABD'deki 15 transplantasyon merkezinden toplanan, 1603 solid organ alıcısından dokümante edilmiş 1208 kanıtlanmış ya da muhtemel İFİ vakasını içeren 12 aylık sağkalım verisi.

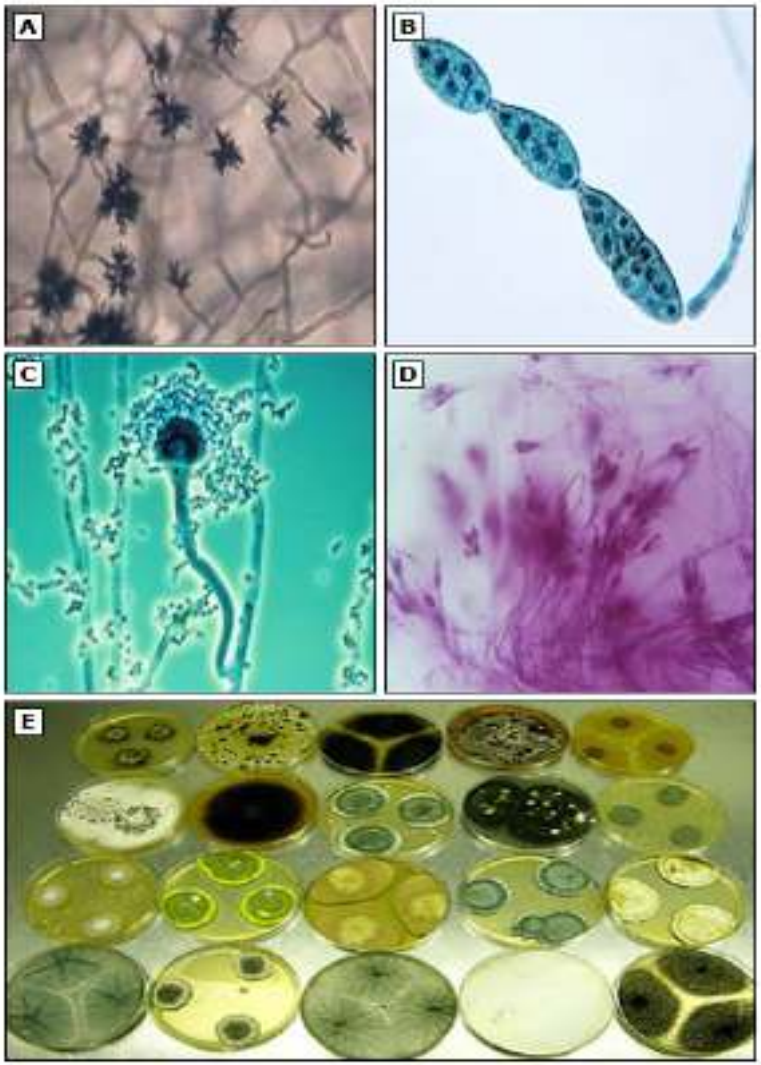
1.Pappas PG et al. Clinical Infectious Diseases 2010; 50:1101–1111.

Diğer küfler

- *Alternaria* spp.
- *Pseudallescheria/Scedosporium* spp.
- *Paecilomyces* spp.
- *Fusarium* spp.
- *Phialophora* spp.

- Riches ML, Trifilio S, Chen M, et al. Risk factors and impact of non-Aspergillus mold infections following allogeneic HCT: a CIBMTR infection and immune reconstitution analysis. Bone Marrow Transplant. 2016;51:277–282

Mold spores



(A) *Cladosporium* spp.

(B) *Alternaria* spp.

(C) *Aspergillus* spp.

(D) *Penicillium* spp.

(E) Various fungi (*Aspergillus* and *Penicillium*) in culture.

Diğer küfler

- *Aspergillus* olmayan küfler nadirdir, yüksek mortaliteye yol açarlar.
- Doku kesitlerinde *Aspergillus* hifalarından ayırt edilemezler.
- Kimlik tespiti için kültür gereklidir.

- Riches ML, Trifilio S, Chen M, et al. Risk factors and impact of non-Aspergillus mold infections following allogeneic HCT: a CIBMTR infection and immune reconstitution analysis. Bone Marrow Transplant. 2016;51:277–282

Diğer küfler

- Allojenik hematopoetik kök hücre nakli (HKHN)'nden sonra 100 gün içinde en sık görülen dissemine fusariosis de pozitif kan kültürleri, cilt lezyonları veya endoftalmi görülür.

- Tedavide, antifungal tedaviye ek olarak nötrofil iyileşmesi gerekir.

- Riches ML, Trifilio S, Chen M, et al. Risk factors and impact of non-Aspergillus mold infections following allogeneic HCT: a CIBMTR infection and immune reconstitution analysis. Bone Marrow Transplant. 2016;51:277–282.
- Nucci M, Marr KA, Queiroz-Telles F, et al. Fusarium infection in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2004;38:1237–1242

Diğer küfler

- Mukormikoz HKHN‘nden sonra nadirdir (allojenik %0,58 ve otolog <%0,1 yılda).
- Klinik olarak aspergillozu taklit eder.
- HKHN‘nden uzun süre sonra ortaya çıkabilir.

- Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001-2006.

Diğer küfler

- Akut veya kronik GVHD
- Steroid kullanımı
- Diyabet
- HKHN sırasında ilerlemiş hastalık
- İleri yaş mukormikoz için risk faktörleridir.

- Riches ML, Trifilio S, Chen M, et al. Risk factors and impact of non-Aspergillus mold infections following allogeneic HCT: a CIBMTR infection and immune reconstitution analysis. Bone Marrow Transplant. 2016;51:277–282

Diğer küfler

- Posakonazol, amfoterisin B'ye yanıt sonrasında belirli *Mucorales* türlerinde etkili bir idame tedavisi olabilir.

- İsavukonazol, invaziv mukormikoz tedavisinde FDA onaylıdır.

- van Burik JA, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis. 2006;42:e61–e65.
- Peixoto D, Gagne LS, Hammond SP, et al. Isavuconazole treatment of a patient with disseminated mucormycosis. J Clin Microbiol. 2014;52:1016–1019

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

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Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

	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	

CNS: central nervous system.

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Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

[a]Both comments apply to the oral solution but may not apply to the solid oral formulation.

Diğer küfler

- Koksidioidomikoz
- Histoplazmoz
- Blastomikoz dahil dimorfik mantar enfeksiyonları nadirdir.

Diğer küfler

- 2003-2013 yılları arasında HKHN alıcılarında koksidioidomikoz insidansının %2,3 (11/426) ve genel mortalitenin %55 olduğu bildirilmiştir.

- Mendoza N, Noel P, Blair JE. Diagnosis, treatment, and outcomes of coccidioidomycosis in allogeneic stem cell transplantation. Transpl Infect Dis. 2015;17:380–388.

TEŞEKKÜR EDERİM….