

ZORLU MANTAR ENFEKSİYONLARI: Aspergillus türleri

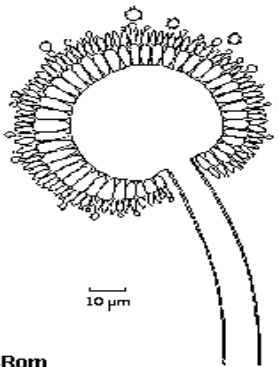


Dr. Nihal Pişkin
Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi
27 Mayıs 2022
10. EKMUD Bilimsel Kongresi, ANTALYA



Aspergilluslar

- Hyalohypomyces grubunda yer alır
- Hifleri septalı olup, in vivo pigmentsiz
- Adlandırma
 - Konidiyal özellik
 - Cinsel yapıları
- 700 tür, 19 tür olası etken



© Fungi-Rom



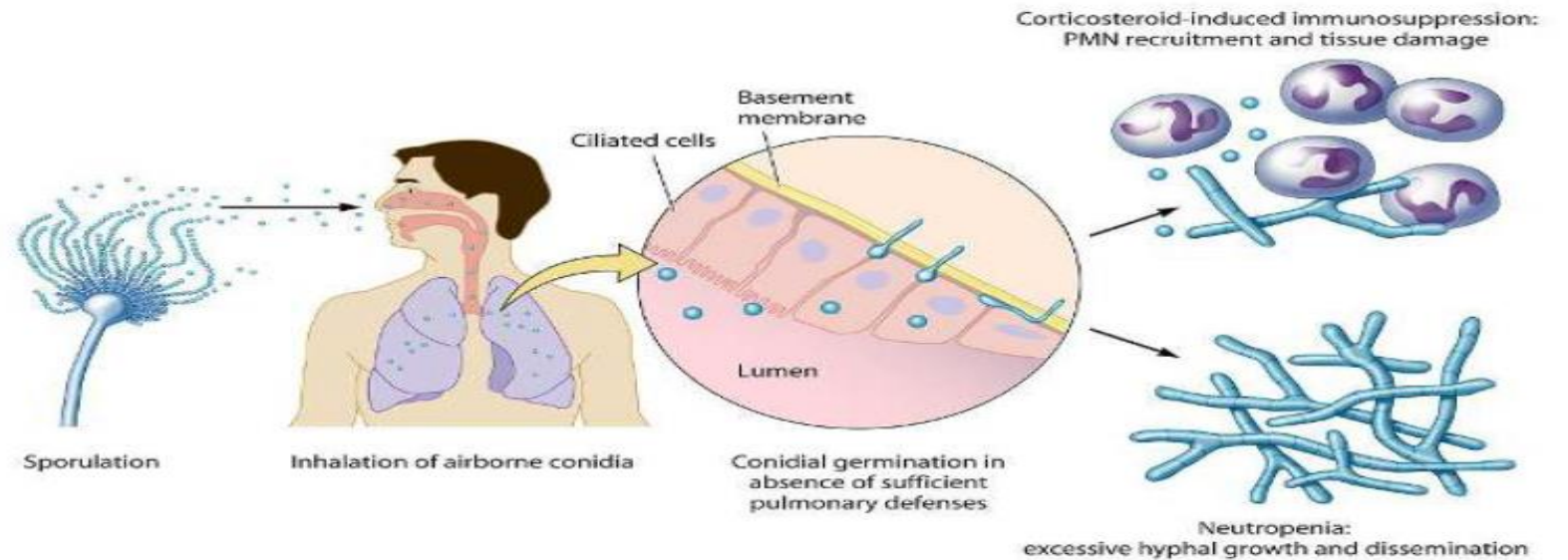
© Fungi-Rom

- *A. fumigatus*; en sık
- *A. flavus*; en allerjik
- *A. niger*
- *A. terreus*; en dirençli

- *A. fumigatus* dışındaki türlerde artış (*A. terreus*)

Bulaş

- En sık konidyaların inhalasyonu sonrası akciğerler ve sinüslerde...
- Daha nadiren gastrointestinal sistemden yayılımla veya deriye direkt inokulasyonla!!



conidial clearance, production of inflammation, and killing of invasive forms

Klinik

Pulmoner formlar; *(en sık)*

- Aspergilloma
- Kronik nekrotizan aspergilloz
- İnvazif pulmoner aspergilloz
- Alerjik bronkopulmoner aspergilloz

Ekstrapulmoner formlar;

- Rinosinuzit
- SSS enfeksiyonu
- Endoftalmit
- Endokardit
- Kutanöz aspergilloz
- Gastrointestinal aspergilloz

Tanı

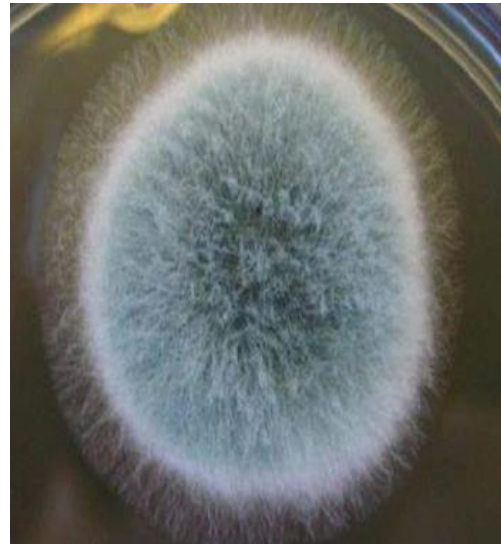
- Klinik



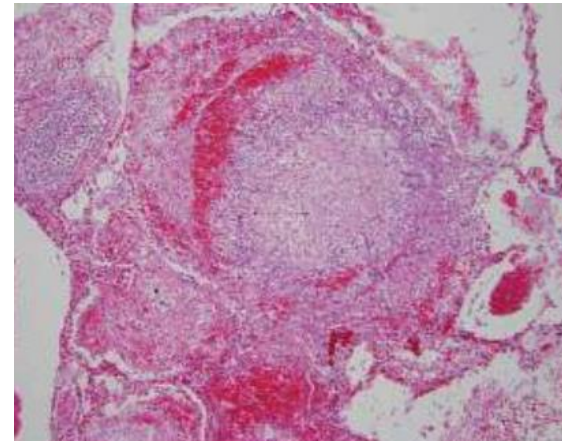
- Radyoloji



- Mikrobiyoloji



- Histopatoloji



Tedavi

Table 1. Antifungal spectrum of activity against common fungi.

Organism	Antifungal agent								
	AmB ^a	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
<i>Aspergillus</i> species	+	-	+	+	+	+	+	+	-
<i>A. flavus</i>	±	-	+	+	+	+	+	+	-
<i>A. fumigatus</i>	+	-	+	+	+	+	+	+	-
<i>A. niger</i>	+	-	±	+	+	+	+	+	-
<i>A. terreus</i>	-	-	+	+	+	+	+	+	-
<i>Candida</i> species	+	+	+	+	+	+	+	+	+
<i>C. albicans</i>	+	+	+	+	+	+	+	+	+
<i>C. glabrata</i>	+	±	±	+	+	+	+	+	+
<i>C. krusei</i>	+	-	±	+	+	+	+	+	±
<i>C. lusitanae</i>	-	+	+	+	+	+	+	+	+
<i>C. parapsilosis</i>	+	+	+	+	+	±	±	±	+
<i>C. tropicalis</i>	+	+	+	+	+	+	+	+	+
<i>Cryptococcus neoformans</i>	+	+	+	+	+	-	-	-	+
<i>Coccidioides</i> species	+	+	+	+	+	± ^a	± ^b	± ^a	-
<i>Blastomyces</i>	+	+	+	+	+	± ^a	± ^b	± ^a	-
<i>Histoplasma</i> species	+	+	+	+	+	± ^a	± ^b	± ^a	-
<i>Fusarium</i> species	±	-	-	+	+	-	-	-	-
<i>Scedosporium apiospermum</i>	±	-	±	+	+	-	-	-	-
<i>Scedosporium prolificans</i>	-	-	-	±	±	-	-	-	-
Zygomycetes	±	-	-	-	+	-	-	-	-

Aspergillus türleri neden zorlu?

Zorlu

Baskı yapabilecek ölçüde güçlü, kuvvetli, şiddetli... (TDK)

Aspergillus türleri neden zorlu??

a) Prevalans??

b) Konakçı özellikleri??

c) Tanısal yöntemler??

d) Tedavi??

e) Hepsi



Review

Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision

Fungal Disease	Annual Incidence	Global Burden	Comments
Superficial			
Skin, hair, nail		-1,000,000,000	
Fungal keratitis		-1,000,000	
Mucosal			
Oral candidiasis	-2,000,000		HIV only, 90% of those not on ARVs
Oesophageal candidiasis	-1,300,000		HIV only, 20% on those with CD4 counts <200 and 5% of those on ARVs
Vulvovaginal candidiasis episode			70% affected in their lifetime
Recurrent vulvovaginal candidiasis		-134,000,000	Annual prevalence. Nearly 500 million lifetime experience
Allergic			
Allergic bronchopulmonary aspergillosis in asthma		-4,800,000	Adults only, rare in children
Allergic bronchopulmonary aspergillosis in cystic fibrosis		-6675	Adults only, starts from age 4
Severe asthma with fungal sensitisation		-6,500,000	Adults only, probably uncommon in children
Fungal rhinosinusitis		-12,000,000	
Chronic severe			
Chronic pulmonary aspergillosis		-3,000,000	
Mycetoma		-9000	1950–2013 case reports, NTD
Chromoblastomycosis		>10,000	Limited data and uncommon, NTD
Coccidioidomycosis		-25,000	
Paracoccidioidomycosis		-4000	
Blastomycosis		-3000	
<i>Histoplasma</i> infection	-500,000	-25,000	Most of the new infections are asymptomatic based on skin testing
Sporotrichosis	>40,000		Very limited global data. Very common in hyper endemic regions of Peru, Brazil and Mexico
Acute invasive			
Invasive candidiasis	-750,000		Includes 60,000–100,000 cases of intra-abdominal candidiasis
Invasive aspergillosis	>300,000		From about 10 million at risk annually
<i>Pneumocystis jirovecii</i> pneumonia in AIDS and non-AIDS	-500,000		
Cryptococcosis in AIDS	-223,000		HIV-related, up to another 10% non-HIV
Mucormycosis	>10,000		Based on French data = 4200. Based on Indian data = 910,000
Disseminated histoplasmosis	-100,000		No reliable estimates
Talaromycosis *	-8000		SE Asia only;

- Fungal enfeksiyonlar > 1 milyar insanı etkiliyor...
- Her yıl > 1.5 milyon ölüm...
- **3.000.000 kronik pulmoner aspergilloz**
- 5.000.000 alerjik bronkopulmoner aspergilloz
- **> 300.000 invazif aspergilloz**
 - Mortalite % 30-80

Konakçı faktörleri

M. KOUSHA ET AL.

REVIEW: PULMONARY ASPERGILLOSIS

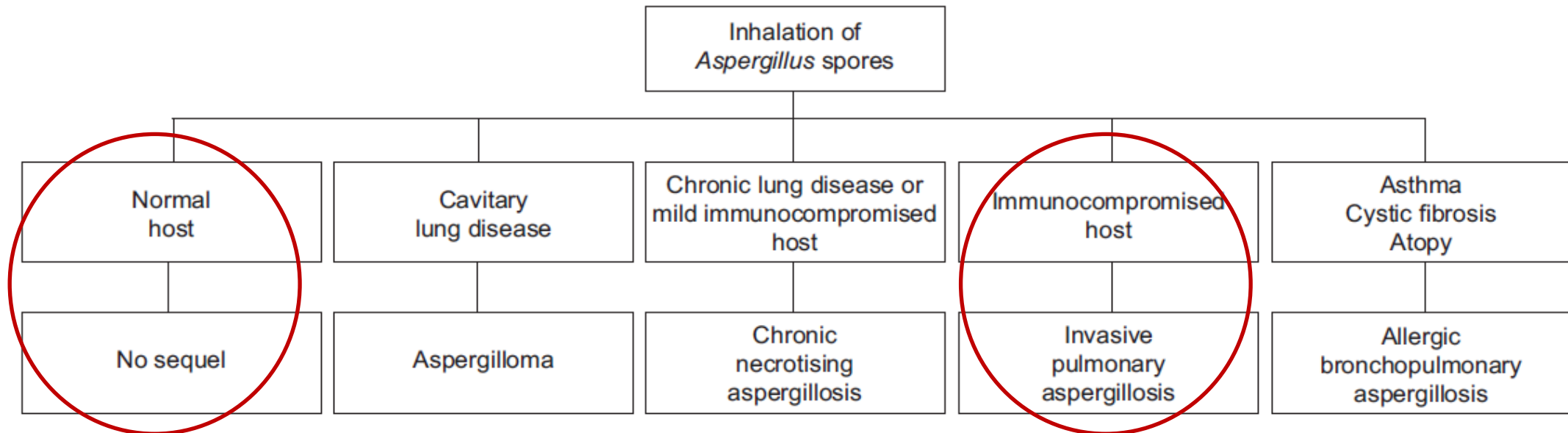


FIGURE 1. The spectrum of pulmonary aspergillosis.

Risk faktörleri

- Klasik risk faktörleri
 - Ciddi ve uzamış nötropeni (AML, AlloHSCT)
 - Yüksek doz steroid kullanımı
 - Hücresel immun yanıtta bozulma yaratan durumlar ve/veya ilaçlar (Otoimmün hastalıkların ve organ rejeksiyonlarının tedavisinde kullanılan immunsupresifler, AIDS)

Her yıl > 30 milyon insan yoğun steroid ve diğer immunsupresif tedavilerin yoğun kullanımına bağlı risk altında....

Bağıışıklığı Baskılanmış Hastalarda İnvazif Fungal Enfeksiyon Riski

■ *Düşük risk*

- Otolog HKHT
- Hodgkin lenfoma
- KML
- Solid tümör
- Miyeloma
- Renal transplant
- Kronik immünolojik hastalık
- SLE

■ *Orta risk*

- ALL
- KLL
- Lenfoma
- AIDS
- Miyelodisplastik sendromlar

■ *Yüksek risk*

- **AML**
- **Allojeneik HKHT**
- **Kalp, AC veya KC transplant**

Risk faktörleri

- İmmünespresyonu olmayan konakta ortaya çıkan risk faktörleri
 - KOAH
 - YBÜ yatışı
 - Viral enfeksiyonlar (influenza*, RSV, SARS-CoV-2**)

Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

Alexander F A D Schauwvlieghe*, Bart J A Rijnders*, Nele Philips, Rosanne Verwijs, Lore Vanderbeke, Carla Van Tienen, Katrien Lagrou,

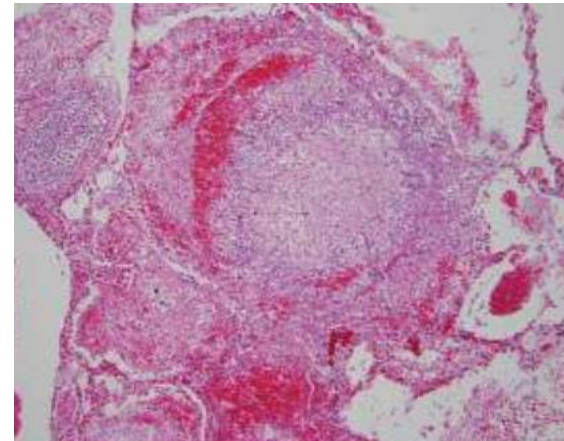
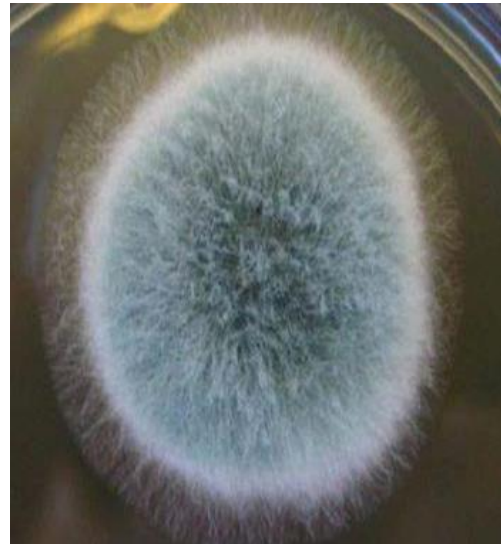
- Temmuz 2016 - Ocak 2019
- YBÜ'de influenza tanısıyla interne edilen 432 hasta
- 83'ünde (% 19) IPA...
 - İmmünesupresyonu olmayanlarda %14 IPA (45/315 hasta)
- IPA gelişenlerde mortalite % 51, gelişmeyenlerde % 28!!!

A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit

- 135 hasta
- IFI insidansı % 26.7
 - Aspergilloz % 14.1, maya enfeksiyonları % 12.6
 - Steroid kullanımı ($p=0.007$) ve KOAH ($p=0.05$) aspergilloz riski ile ilişkili!!!
- Mortalite % 38
 - Fungal enfeksiyonu olanlarda % 53, olmayanlarda % 31 ($p=0.0387$)
 - Antifungal alanlarda % 38.5, almayanlarda % 90 ($p=0.008$)

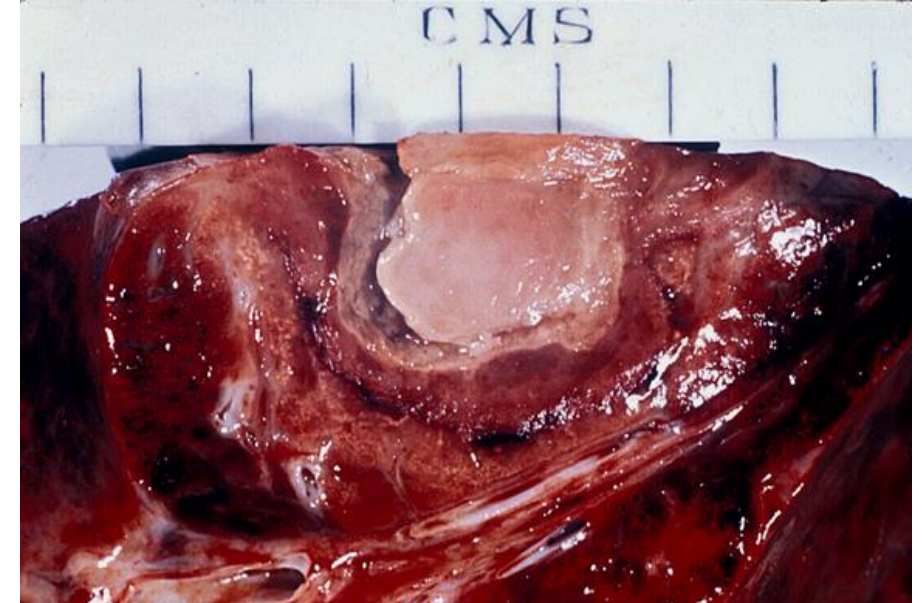
Tanı

- Klinik
- Radyoloji
- Mikrobiyoloji
- Histopatoloji



Tanı - Klinik

- Klasik triad;
 - Ateş
 - Plöritik ağrı
 - Hemoptizi
- Klinik bulgu vermeyebilir !!!!
- Post-mortem tanı konabilir☹



Tanı - Radyoloji

- Direkt grafiler non-spesifik!!
- BT; fokal lezyonları göstermede değerli!!
- Radyolojik anormallikler hastalığın tipine ve konak faktörlerine göre değişkenlik göstermekte...

Increasing Volume and Changing Characteristics of Invasive Pulmonary Aspergillosis on Sequential Thoracic Computed Tomography Scans in Patients With Neutropenia

By Denis Caillot, Jean-Francois Couaillier, Alain Bernard, Olivier Casasnovas, David W. Denning, Lionel Mannone, Jose Lopez, Gerard Couillault, Françoise Piard, Odile Vagner, and Henri Guy

Seri BT !!!

Halo belirtisi

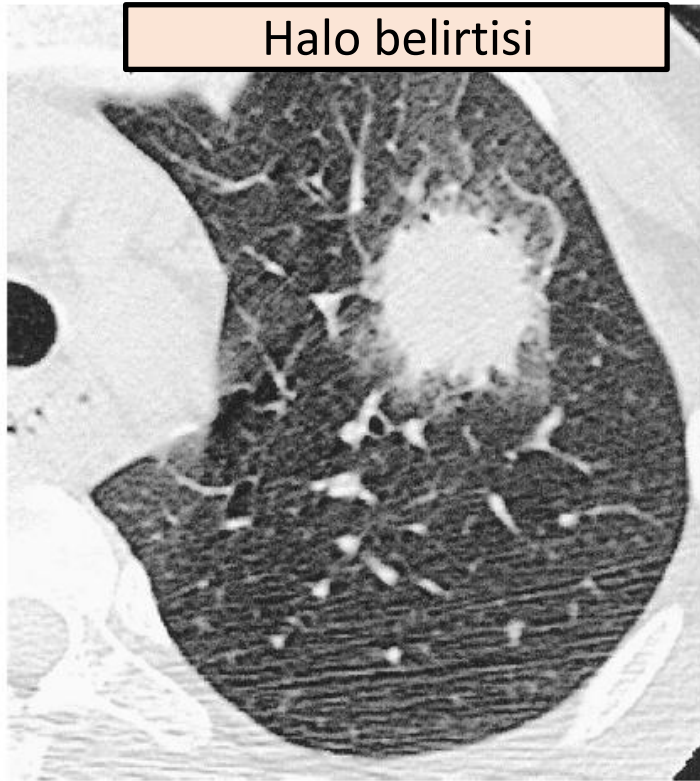


Fig 1. CT halo sign. This first thoracic CT scan (day 0) was performed in a patient with febrile neutropenic leukemia. The ground glass attenuation surrounding the nodule was considered a typical halo sign. The diagnosis of IPA was considered highly likely, and antifungal treatment was started.

Konsolidasyon

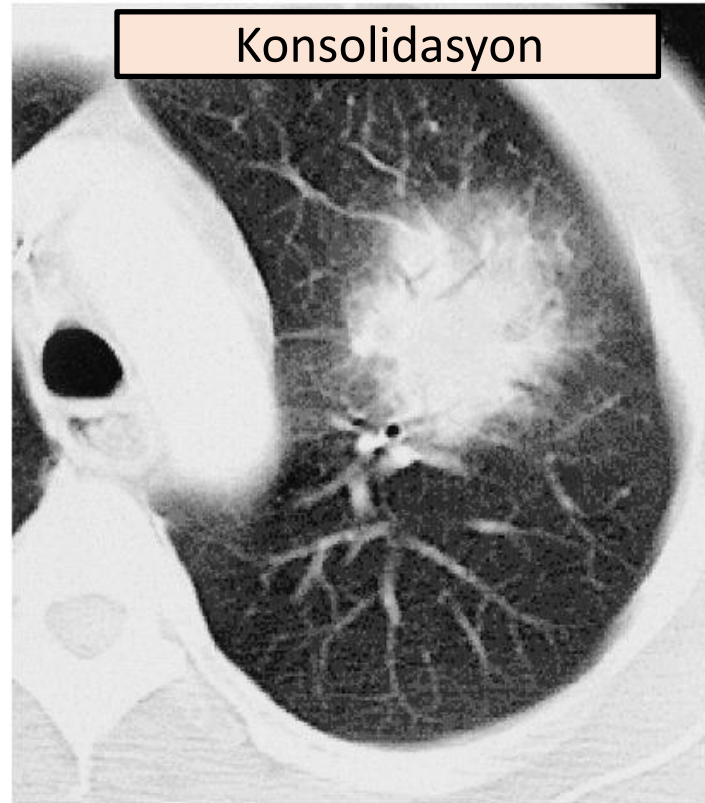


Fig 2. Low specific CT image. A new CT scan was performed 4 days later (day 4). It showed an increase of the left-sided aspergillary mass with a partial loss of peripheral ground glass attenuation.

Hava hilal belirtisi

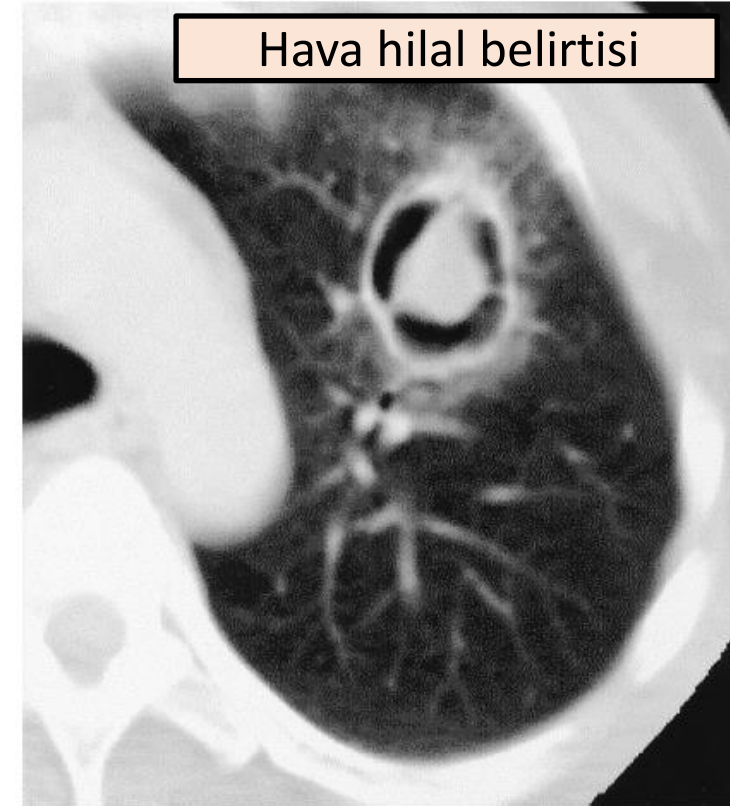
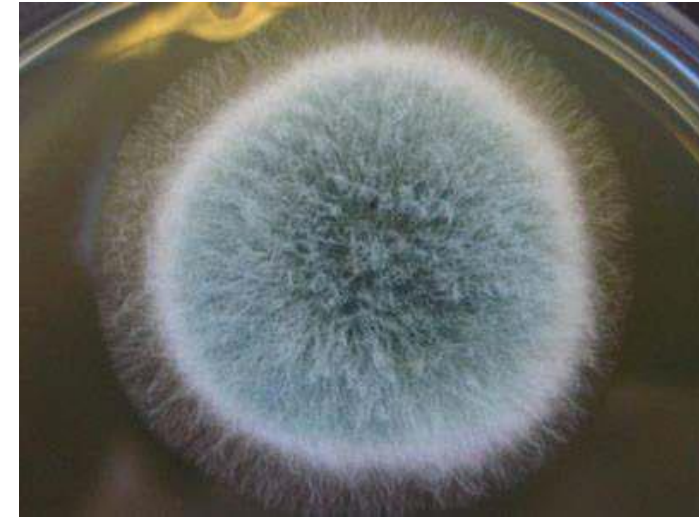
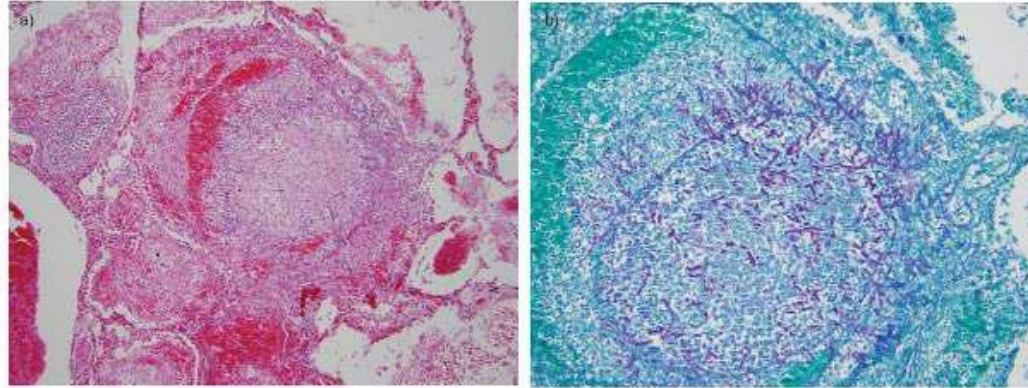


Fig 3. CT air-crescent sign. Marrow recovery occurred on day 7. On day 10, an air-crescent sign appeared on CT scan. A surgical resection confirmed the diagnosis of IPA. Subsequently, the patient received itraconazole for 12 months, and 30 months later, she was well and alive.

Tanı - Mikrobiyoloji

- Kültür ; Tek başına kültür pozitifliği duyarlı değil...
 - %25-50 dökumante invazif aspergilloz olgusunda kültür negatif...
- Histopatoloji +
- Kültür

Kültürde *Aspergillus* spp üremesi ve histopatolojik olarak dokuda hifal invazyonun birlikte gösterilmesi ile kesin tanı!!!



Tanı

- Çoğu olguda biyopsi yapılamamakta;
 - Biyolojik belirteçler
 - Galaktomannan
 - B-D-Glucan
 - PCR
 - Diğer metodlar



Galaktomannan antijen testi

- Galaktomannan; Aspergillus hücre duvarında bulunan bir polisakkarid...
- Galaktomannan EIA; optik dansite (OD index) olarak ölçülmekte....
 - FDA; serum ve BAL örneklerinde pozitif sonuç için OD indeks ≥ 0.5 değerini belirlemiş...
 - EORTC/MSGERC daha kesin tanısal değer olarak OD indeks ≥ 1 değerini önermekte....
- Sensitivite öncesinde antifungal tedavi varlığında düşmekte....
- Piperasilin tazobaktam kullananlarda bildirilen yalancı pozitiflik yeni preparatlarda çok nadir olarak bildirilmekte.... Benzer durum amoksisilin-klavulonat i.v. formülasyonları için de bildirilmiş....

Galactomannan detection for invasive aspergillosis in immunocompromised patients (Review)

Leeflang MMG, Debets-Ossenkopp YJ, Wang J, Visser CE, Scholten RJPM, Hooft L, Bijlmer HA, Reitsma JB, Zhang M, Bossuyt PMM, Vandenbroucke-Grauls CM

Main results

We included 54 studies in the review (50 in the meta-analyses), containing 5660 patients, of whom 586 had proven or probable invasive aspergillosis. When using an optical density index (ODI) of 0.5 as a cut-off value, the sensitivity of the test was 78% (70% to 85%) and the specificity was 85% (78% to 91%). At a cut-off value of 1.0 ODI, the sensitivity was 71% (63% to 78%) and the specificity was 90% (86% to 93%). At a cut-off value of 1.5 ODI, the sensitivity was 63% (49% to 78%) and the specificity was 93% (89% to 97%). None of the potential sources of heterogeneity had a statistically significant effect on either sensitivity or specificity.

- 54 çalışma, 5660 immunsuprese hastada 586 IA olgusunun değerlendirildiği bir metaanalizde;
- OD index > 0.5 ile sensitivite % 82, spesifite % 81

Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis

Christopher D. Pfeiffer,¹ Jason P. Fine,² and Nasia Safdar¹

Table 4. Pooled sensitivity and specificity of the galactomannan assay for diagnosis of invasive aspergillosis (IA).

Studies	Cases of proven IA				Cases of proven or probable IA			
	TP/(TP+FP)	Pooled sensitivity (95% CI)	TN/(TN+FP)	Pooled specificity (95% CI)	TP/(TP+FN)	Pooled sensitivity (95% CI)	TN/(TN+FP)	Pooled specificity (95% CI)
All	163/229	0.71 (0.68–0.74)	3601/4055	0.89 (0.88–0.90)	250/407	0.61 (0.59–0.63)	2839/3060	0.93 (0.92–0.94)
Studies limited to patients with hematological malignancy	106/152	0.70 (0.62–0.77)	2570/2808	0.92 (0.90–0.93)	177/304	0.58 (0.52–0.64)	2324/2457	0.95 (0.94–0.96)
Studies limited to patients undergoing BMT	49/60	0.82 (0.70–0.90)	722/843	0.86 (0.83–0.88)	32/49	0.65 (0.60–0.78)	17/26	0.65 (0.44–0.83)
Studies limited to solid-organ transplant recipients	2/9	0.22 (0.03–0.60)	180/215	0.84 (0.78–0.88)	9/22	0.41 (0.21–0.64)	210/247	0.85 (0.80–0.89)
Studies using EORTC/MSG criteria	74/116	0.64 (0.54–0.73)	2549/2869	0.89 (0.88–0.90)	211/354	0.60 (0.54–0.65)	2628/2823	0.93 (0.92–0.94)
Studies not using EORTC/MSG criteria	89/113	0.79 (0.70–0.86)	1052/1186	0.89 (0.87–0.90)	39/53	0.74 (0.60–0.85)	211/237	0.89 (0.84–0.93)
Studies involving pediatric population only	8/9	0.89 (0.51–1.00)	316/370	0.85 (0.85–0.89)	11/12	0.92 (0.82–1.00)	12/20	0.60 (0.36–0.81)
Studies involving adult population only	58/93	0.62 (0.52–0.72)	1211/1398	0.87 (0.85–0.88)	102/140	0.73 (.46-.61)	802/889	0.90 (.88–0.92)
Studies of both pediatric and adult populations	70/93	0.75 (0.65–0.84)	1726/1875	0.92 (0.91–0.93)	92/196	0.47 (0.40–0.54)	1601/1701	0.94 (0.93–0.95)
Studies using a cutoff value of 0.5 for defining positivity	3/11	0.27 (0.06–0.61)	27/341	0.79 (0.74–0.83)	69/87	0.79 (0.69–0.87)	493/571	0.86 (0.83–0.89)
Studies using a cutoff value of 1.0 for defining positivity	85/107	0.79 (0.71–0.87)	1385/1598	0.87 (0.85–0.88)	103/159	0.65 (0.57–0.72)	1163/1242	0.94 (0.92–0.95)
Studies using a cutoff value of 1.5 for defining positivity	75/111	0.68 (0.58–0.76)	1946/2116	0.92 (0.91–0.93)	78/161	0.48 (0.41–0.56)	1183/1247	0.95 (0.93–0.96)

- 17 çalışmanın değerlendirildiği bir metaanalizde; hasta grupları arasında testin etkinliği değişebilmekte;
- Hematolojik malignite veya kemik iliği nakli alıcıları > Solid organ nakli

Beta-D-glukan testi

- 1,3-Beta-D-glucan pek çok mantarın hücre duvarı komponenti
- Beta-D-glukan testi; Aspergillus için spesifik değil; kandidiyaz, P. jirovecii gibi invazif fungal enfeksiyonlarda da pozitif...
- Farklı ticari kitler var; cut-off değerleri daha çok invazif kandidiyaz için belirlenmiş...
- IVIG, albümin, sellülöz membranlı hemodiyaliz, i.v. amoksisilin-klavulonat formülasyonları yalancı pozitifliğe neden olabilir.....

β -D-Glucan Assay for the Diagnosis of Invasive Fungal Infections: A Meta-analysis

Drosos E. Karageorgopoulos,^{1,2} Evidiki K. Vouloumanou,¹ Fotinie Ntziora,^{1,2} Argyris Michalopoulos,^{1,3} Petros I. Rafailidis,^{1,4} and Matthew E. Falagas^{1,4,5}

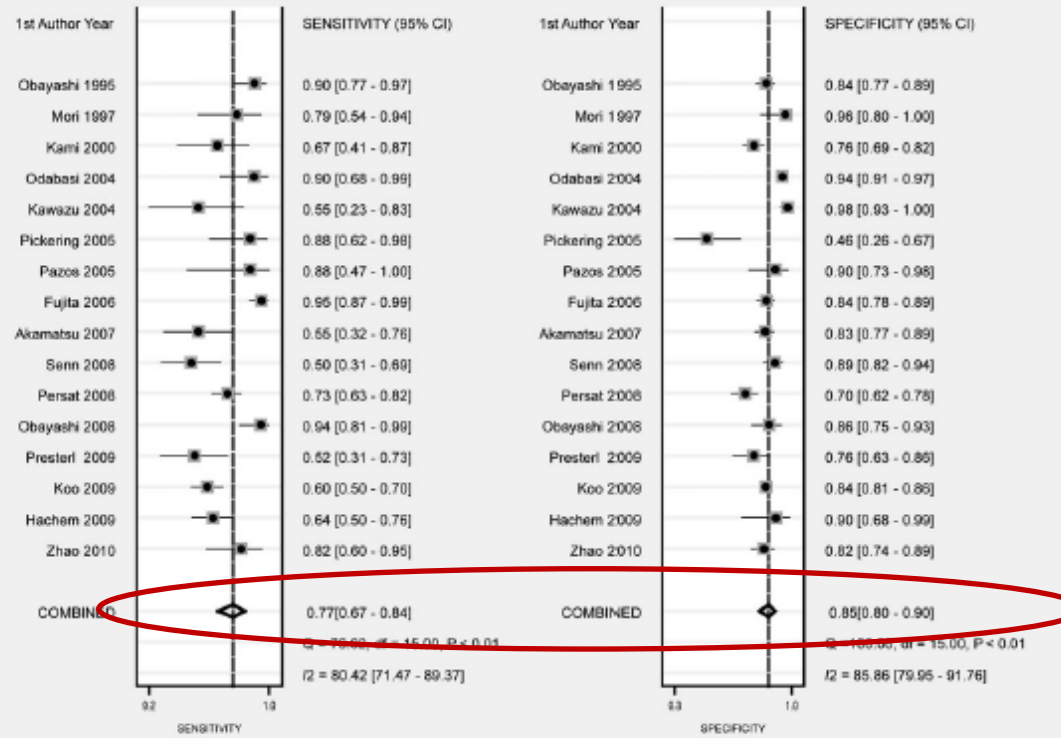


Figure 4. Forest plot of the pooled sensitivity and specificity of measuring serum or plasma (1→3)- β -D-glucan levels for the diagnosis of proven or probable invasive fungal infections. The circles in squares and the horizontal lines represent the point estimate and 95% confidence interval, respectively, for each included study; the dotted line represents the pooled estimate; and the diamond represents the 95% confidence interval of the pooled estimate.

- İnvazif fungal enfeksiyon tanısında Beta-D-glukan testinin değerlendirildiği 16 çalışmayı içeren bir metaanalizde ortalama
- Sensitivite % 77
- Spesifite % 85

β -Glucan Antigenemia Assay for the Diagnosis of Invasive Fungal Infections in Patients With Hematological Malignancies: A Systematic Review and Meta-Analysis of Cohort Studies From the Third European Conference on Infections in Leukemia (ECIL-3)

Frédéric Lamothe,^{1,2} Mario Cruciani,^{2,4} Carlo Mengoli,³ Elio Castagnola,⁴ Olivier Lortholary,^{5,6,7} Malcolm Richardson,⁸ and Oscar Marchetti,¹ on behalf of the Third European Conference on Infections in Leukemia (ECIL-3)

Methods. Studies reporting the performance of BG antigenemia assays for the diagnosis of IFI (European Organization for Research and Treatment of Cancer and Mycoses Study Group criteria) in hemato-oncological patients were identified. The analysis was focused on high-quality cohort studies with exclusion of case-control studies. Meta-analysis was performed by conventional meta-analytical pooling and bivariate analysis.

Results. Six cohort studies were included (1771 adult patients with 414 IFIs of which 215 were proven or probable). Similar performance was observed among the different BG assays. For the cutoff recommended by the manufacturer, the diagnostic performance of the BG assay in proven or probable IFI was better with 2 consecutive positive test results (diagnostic odds ratio for 2 consecutive vs one single positive results, 111.8 [95% confidence interval {CI}, 38.6–324.1] vs 16.3 [95% CI, 6.5–40.8], respectively; heterogeneity index for 2 consecutive vs one single positive results, 0% vs 72.6%, respectively). For 2 consecutive tests, sensitivity and specificity were 49.6% (95% CI, 34.0%–65.3%) and 98.9% (95% CI, 97.4%–99.5%), respectively. Estimated positive and negative predictive values for an IFI prevalence of 10% were 83.5% and 94.6%, respectively.

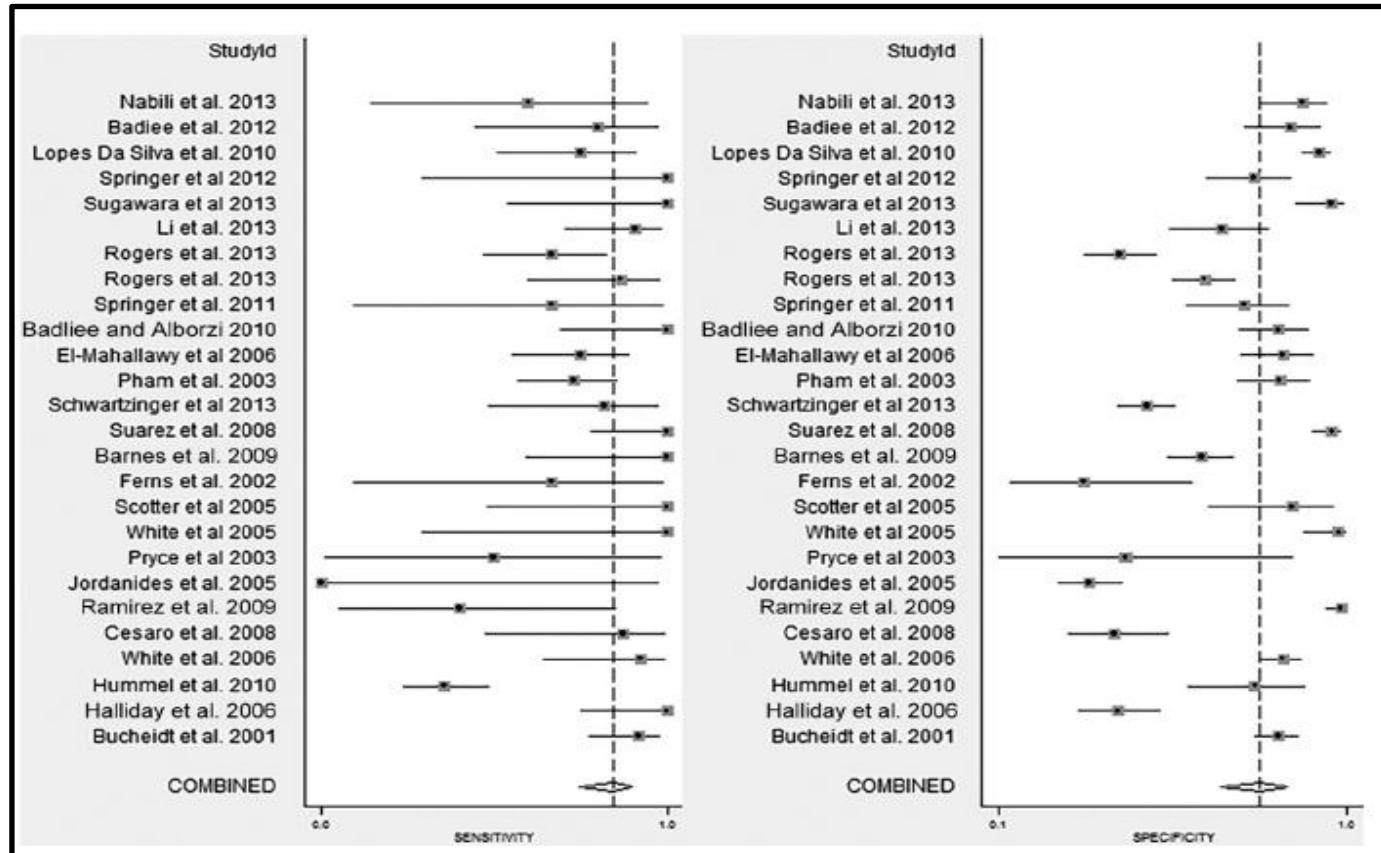
- Hematolojik malignitesi olan hastalarda yapılan 6 çalışmanın değerlendirildiği bir metaanalizde;
- Ardışık 2 test daha değerli!!!
- Sensitivite % 50
- Spesifite % 99

PCR

- İnvazif aspergillozdan şüphelenildiğinde diğer bio-belirteçlerle birlikte bakılması önerilmekte....
- Serum, plazma, tam kan veya BAL da bakılabilmekte...
- 2 ardışık test sonucu daha değerli....

PCR in Diagnosis of Invasive Aspergillosis: a Meta-Analysis of Diagnostic Performance

Marios Arvanitis,^{a,b} Panayiotis D. Ziakas,^{a,b} Ioannis M. Zacharioudakis,^{a,b} Fainareti N. Zervou,^{a,b} Angela M. Caliendo,^{a,b} Eleftherios Mylonakis^{a,b}



25 çalışmanın değerlendirildiği bir çalışmada PCR'in invazif aspergillozu saptamada sensitivitesi % 84, spesifitesi % 76

EORTC tanımları

Şüpheli

- Konakçı faktörleri
- + Klinik faktörler

Olası

- Konakçı faktörleri
- + Klinik faktörler
- + Mikrobiyolojik faktörler

Kesin

- ± Konakçı faktörü
- Histopatoloji
- Kültür
- Dokuda PCR

Clinical Infectious Diseases

MAJOR ARTICLE

 **IDSA**
Infectious Diseases Society of America

 **hivma**
hiv medicine association

 **OXFORD**

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

Table 1. Criteria for Proven Invasive Fungal Disease

Fungus	Microscopic Analysis: Sterile Material	Culture: Sterile Material	Blood	Serology	Tissue Nucleic Acid Diagnosis
Molds ^a	Histopathologic, cytopathologic, or direct microscopic examination ^b of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine	Blood culture that yields a mold ^c (eg, <i>Fusarium</i> species) in the context of a compatible infectious disease process	Not applicable	Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue

Table 2. Probable Invasive Pulmonary Mold Diseases

Host factors

Recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/L [<500 neutrophils/ mm^3] for >10 days) temporally related to the onset of invasive fungal disease

Hematologic malignancy^a

Receipt of an allogeneic stem cell transplant

Receipt of a solid organ transplant

Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥ 0.3 mg/kg corticosteroids for ≥ 3 weeks in the past 60 days

Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor- α blockade, or anti-CD28-specific monoclonal antibodies, immunosuppressive during the past 90 days

Treatment with recognized B-cell immunosuppressants, such as tyrosine kinase inhibitors, eg, ibrutinib

Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)

Acute graft-versus-host disease grade III or IV involving the lung or liver that is refractory to first-line treatment with corticosteroids

Clinical features

Pulmonary aspergillosis

The presence of 1 of the following 4 patterns on CT:

- Dense, well-circumscribed lesions(s) with or without a halo sign
- Air crescent sign
- Cavity
- Wedge-shaped and segmental or lobar consolidation

Other pulmonary mold diseases

As for pulmonary aspergillosis but also including a reverse halo sign

Tracheobronchitis

Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

Sino-nasal diseases

- Acute localized pain (including pain radiating to the eye)
- Nasal ulcer with black eschar
- Extension from the paranasal sinus across bony barriers, including into the orbit

Central nervous system infection

1 of the following 2 signs:

- Focal lesions on imaging
- Meningeal enhancement on magnetic resonance imaging or CT

Mycological evidence

Any mold, for example, *Aspergillus*, *Fusarium*, *Scedosporium* species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate

Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold

Tracheobronchitis

Aspergillus recovered by culture of BAL or bronchial brush

Microscopic detection of fungal elements in BAL or bronchial brush indicating a mold

Sino-nasal diseases

Mold recovered by culture of sinus aspirate samples

Microscopic detection of fungal elements in sinus aspirate samples indicating a mold

Aspergillosis only

Galactomannan antigen

Antigen detected in plasma, serum, BAL, or CSF

Any 1 of the following:

- Single serum or plasma: ≥ 1.0
- BAL fluid: ≥ 1.0
- Single serum or plasma: ≥ 0.7 and BAL fluid ≥ 0.8

Aspergillus PCR

Any 1 of the following:

- Plasma, serum, or whole blood 2 or more consecutive PCR tests positive
- BAL fluid 2 or more duplicate PCR tests positive
- At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

Aspergillus species recovered by culture from sputum, BAL, bronchial brush, or aspirate

(1,3)-beta-D glucan mikrobiyolojik kanıt olarak değerlendirilmemekte!!

Tedavi

Guideline

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



Sanjeet S. Dadwal^{1,*}, Tobias M. Hohl², Cynthia E. Fisher³, Michael Boeckh⁴, Genofeva Papanicolaou²,
Paul A. Carpenter⁵, Brian T. Fisher⁶, Monica A. Slavin⁷, D.P. Kontoyiannis⁸

Clinical Infectious Diseases Advance Access published June 29, 2016

IDS A GUIDELINE



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

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



ELSEVIER

Contents lists available at [ScienceDirect](#)

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

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

Tedavi

- İlk basamak tedavide AI kanıt düzeyinde vorikonazol, isovukanozol*
- Kullanılmadığı durumda ve kurtarma tedavisinde Lip-AmB, isovukanozol*, posakonazol*
- Ekinokandinler yalnızca kurtarma tedavisinde kombinasyonda önerilir.

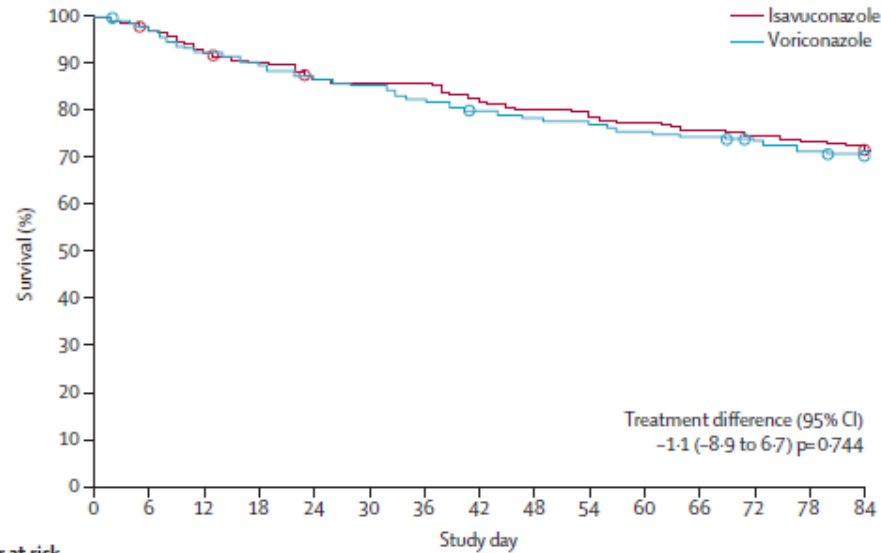
Posakonazol

- Oral süspansiyon; 2005'de FDA onay! (>13 yaş)
 - Günde 3-4 defa kullanım, yağlı yiyeceklerle birlikte alınmalı!
- Posakonazol Tablet; 2013 yılında FDA onay! (>13 yaş)
 - Düşük mide pH'ında stabil kalıp, ince barsak nötral pH'da açılmakta!
 - Tabletler yiyecekler ile birlikte veya tek başına alınabilir.
- İntravenöz form; 2014 yılında FDA onay! (>18 yaş)
 - Yavaş infüzyonla & santral venöz kateterle verilmeli

İsavukonazol

- İkinci jenerasyon triazol
- Oral ve intravenöz formu; 2015'de FDA onay
 - İsavukonazonyum sülfat 186 mg/kapsül (İsavukonazol 100 mg/kapsül)
 - İsavukonazonyum sülfat 372 mg/flakon (İsavukonazol 200mg/flakon)
- En az 1 saatlik infüzyonla verilir

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Isavuconazole	258	252	240	232	224	220	220	211	206	204	199	195	192	188	185
Voriconazole	258	253	239	233	225	220	213	206	202	199	194	192	188	182	179

Figure 2: Survival from first dose of study drug to day 84

Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

- 2007-2013 arasında, 26 ülkeden 102 merkez
- 516 invaziv Aspergilloz olgusu; % 84 hematolojik maligniteli
- 1:1 randomizasyon (258 isavukonazol:258 vorikonazol)
- Primer sonlanım 42.günde mortalite
 - ISA mortalite %19 (48/258)
 - VOR mortalite %20 (52/258)
- Tedavi sonunda başarı İSA %35, VOR %38.9
- İlaç ilişkili yan etkiler isavukonazol alan 109 (% 42) hastada, vorikonazol alan 155 (% 60) hastada bildirilmiş. (p<0.001).

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

Primer tedavi

- Vorikonazol

Alternatif tedavi

- L-AmB,
- İsavukonazol

Kurtarma tedavisi

- Posakonazol oral süspansiyon
- Posakonazol tablet
- Posakonazol i.v
- Kaspofungin
- Mikafungin
- İtrakonazol
- ABLC

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



EUROPEAN
HEMATOLOGY
ASSOCIATION



Primer tedavi

- Vorikonazol AI
- İsavukonazol AI
 - (En az Vorikonazol kadar etkili, daha iyi tolere)
- L-AmB BI
- ABLC BII
- ABCD CI
- Kaspofungin CII
- İtrakonazol CIII
- Vorikonazol + Anidulafungin CI
- Diğer kombinasyonlar CIII

Kurtarma tedavisi

- Vorikonazol BII (ilk seçenek olarak verilmemişse)
- Posakonazol*,** BII
- Kaspofungin* BII
- L-AmB* BII
- ABLC* BII
- İtrakonazol CIII
- Kombinasyon BII

- *Vorikonazol başarısızlığında veri yok
- **Oral süspansiyon kullanıyorsa serum düzeyi takibi gerekebilir



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

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

Primer tedavi

- Vorikonazol AI
- İsavukonazol AI
- L-AmB BII
- ABLC CIII
- ABCD DI
- Kaspofungin CII
- İtrakonazol CIII
- Vorikonazol + Anidulafungin CI
- Diğer kombinasyonlar CIII



Kurtarma tedavisi

- Farklı bir grup ajanla tedavi...

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial

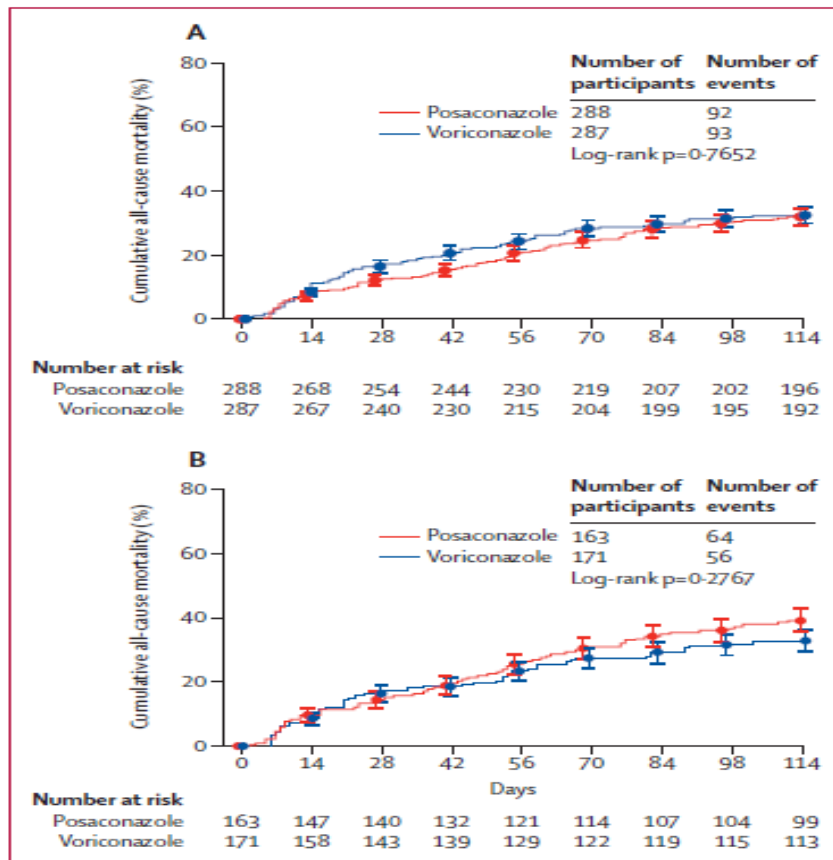


Figure 2: Kaplan-Meier plot for cumulative all-cause mortality up to and including day 114 (A) ITT population. (B) Full analysis set population (ITT with proven or probable invasive aspergillosis). The ITT population included all randomly assigned participants who received one or more dose of study drug. ITT=intention-to-treat.

- 2013-2019 arasında
- 575 invaziv Aspergilloz olgusu; 1.1 randomizasyon (288 posakonazol:287 vorikonazol)
- Primer sonlanım 42.günde mortalite
 - POS mortalite %15 (44/288)
 - VOR mortalite %21 (59/287)
- Kesin ve olası IA olgularında 42. gün mortalite her iki grupta % 19
- İlaç ilişkili yan etkiler posakonazol grubunda % 30, vorikonazol grubunda % 40) hastada bildirilmiş.

Tedavi- Zorluklar

- Yan etkiler
- İlaç etkileşimleri
- İlaç düzeyi monitorizasyonu
- Antifungal duyarlılık

İlaç etkileşimleri

	<u>CYP3A4</u>		<u>CYP2C9</u>		<u>CYP2C19</u>	
	<u>Substrate</u>	<u>Inhibitor</u>	<u>Substrate</u>	<u>Inhibitor</u>	<u>Substrate</u>	<u>Inhibitor</u>
Fluconazole		<u>Moderate</u>		<u>Moderate</u>		<u>Strong</u>
Itraconazole	<u>Major</u>	<u>Strong</u>				
Voriconazole	<u>Minor</u>	<u>Strong</u>	<u>Major</u>	<u>Moderate</u>	<u>Major</u>	<u>Moderate</u>
Posaconazole		<u>Strong</u>				
Ketoconazole	<u>Major</u>	<u>Strong</u>		<u>Moderate</u>		<u>Moderate</u>
Miconazole						
Isavuconazole	<u>Major</u>	<u>Moderate</u>				<u>Weak</u>

Terapötik etkinliği optimize etmek ve potansiyel toksisiteyi önlemek için; *hem azol grubu antifungal ilaçların* (itrakonazol, vorikonazol, posakonazol ve mümkünse isavuconazol) hem de siklosporin, tacrolimus, sirolimus gibi *CYP3A4 ile etkileşime giren ilaçların serum düzeylerini değerlendirmelidir.* (SR; MQE)

İlaç düzeyi monitorizasyonu

Triazollerle tedavi veya uzamış profilaksi almakta olan hastalarda veya azollerle ilaç etkileşimine girebilecek diğer tedavileri almakta olan hastalarda bir kez kararlı duruma ulaşıncaya kadar “*terapötik ilaç düzeyi monitorizasyonu*” önerilmekte.

- Özellikle itrakonazol, vorikonazol ve posakonazolün süspansiyon formları için monitorizasyonun; tedavi etkinliğini arttırdığı, suboptimal ilaç düzeylerine bağlı tedavi başarısızlıklarını ve azollere bağlı toksisiteyi azalttığı yönünde kayda değer çalışmalar mevcut.(SR; MQE)
- Posakonazolün ER ve iv formülasyonları ve isavukonazolün monitorizasyonu ile ilgili ileri çalışmalara ihtiyaç var!

- **Vorikonazol için istenen serum konsantrasyonu 1-5.5 µg/ml**
- **Posakonazol için istenen serum konsantrasyonu tedavi için 1.5-3.75 mg/L, profilaksi için 0.7-3.5 mg/L**
- **4-7. günde bakılması önerilmekte....**

Antifungal duyarlılık

- Üreyen etkenler için *başlangıçta rutin antifungal duyarlılık testlerinin (AFDT) yapılması önerilmemekte!!*
- Referans bir metodla AFDT yapılması; azol-dirençli bir izolatla enfekte olduğundan şüphelenilen veya antifungal tedaviye yanıt vermeyen hastalarda veya epidemiyolojik amaçlarla yapılabilir. (SR; MQE)

Profilaksi

- AML veya MDS: Remisyon–indüksiyon kemoterapisi alan, invazif mantar enfeksiyonu gelişme riski yüksek olan hastalar
- HKHN – GVHH: Hematopoetik kök hücre alıcısı olup, GVHH yönelik olarak yüksek doz immüsupresif tedavi alan ve invazif mantar enfeksiyonu gelişme riski yüksek olan hastalar

- Önerilen ajanlar;
- Posakonazol
- Vorikonazol

Aspergillus türleri neden zorlu?

Sonuç

- Epidemiyolojik, radyolojik, klinik, biyolojik veriler tanıda birlikte kullanılmalı...
- Tıbbi durum ve serum galaktomannan antijen her ikisinin de spesifikliđi konusunda bazı sınırlamalar olmasına rağmen temel yaklaşımda kullanılmalı!
-
- (1→3)-β-D-glukan pan-fungal serum belirteci ancak çok iyi negatif prediktif değere sahip....
- Real-time PCR standardize değil☹

Sonuç

- Solunum yolu örneklerinden fungal kültürler yeterince duyarlı değil 😞
- Histopatoloji aspergilloz tanısında önemli, ancak biyopsi immun suprese hastada her zaman mümkün değil 😞
- Optimal tedavi; hastanın immun durumuna, organ disfonksiyonlarına ve önceki tedavi durumlarına göre şekillenmeli!!!
- İlaç düzeyi monitorizasyonu ve antifungal duyarlılık testlerine ulaşımında sıkıntılar var 😞



Teşekkür ederim