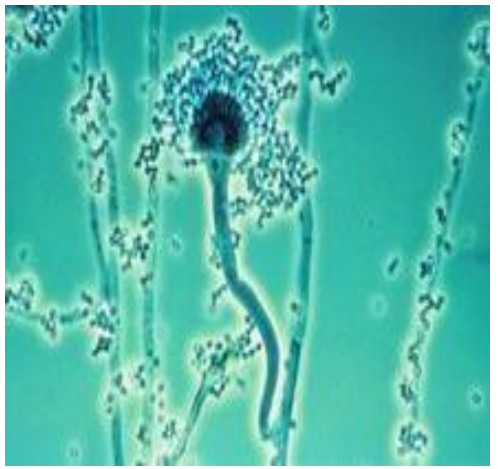
KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Pulmoner Aspergilloz (İstanbul)

Simpozyum

26 Şubat 2019

İNVAZİF PULMONER ASPERGİLLOZ TANI VE TEDAVİSİNDE YENİLİKLER



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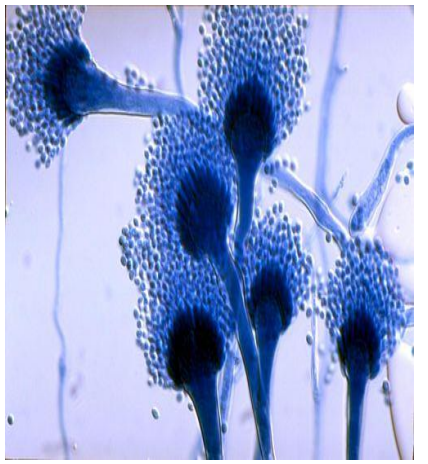
Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji



PLAN

- İPA Tanısı
- İPA Tedavisi
- Rehber Önerileri
- İPA Korunma

Aspergilloz

1. **İnvazif Aspergilloz**
   - **İnvazif Pulmoner Aspergilloz (İPA)**
   - Aspergillus sinüziti
   - Dissemine Aspergilloz
2. **Kronik (saprofitik) Aspergilloz**
3. **Allerjik Aspergilloz**

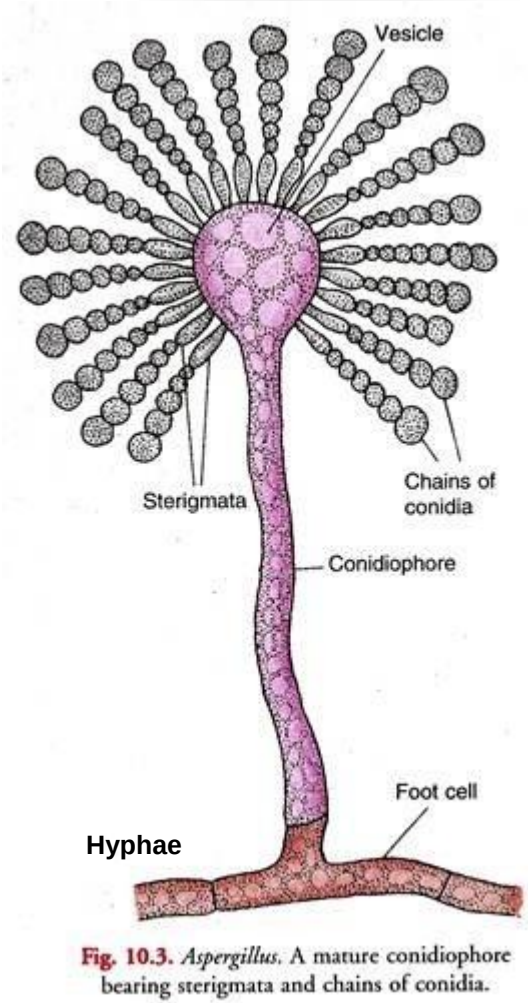


Fig. 10.3. *Aspergillus*. A mature conidiophore bearing sterigmata and chains of conidia.

Konak vs *Aspergillus spp*

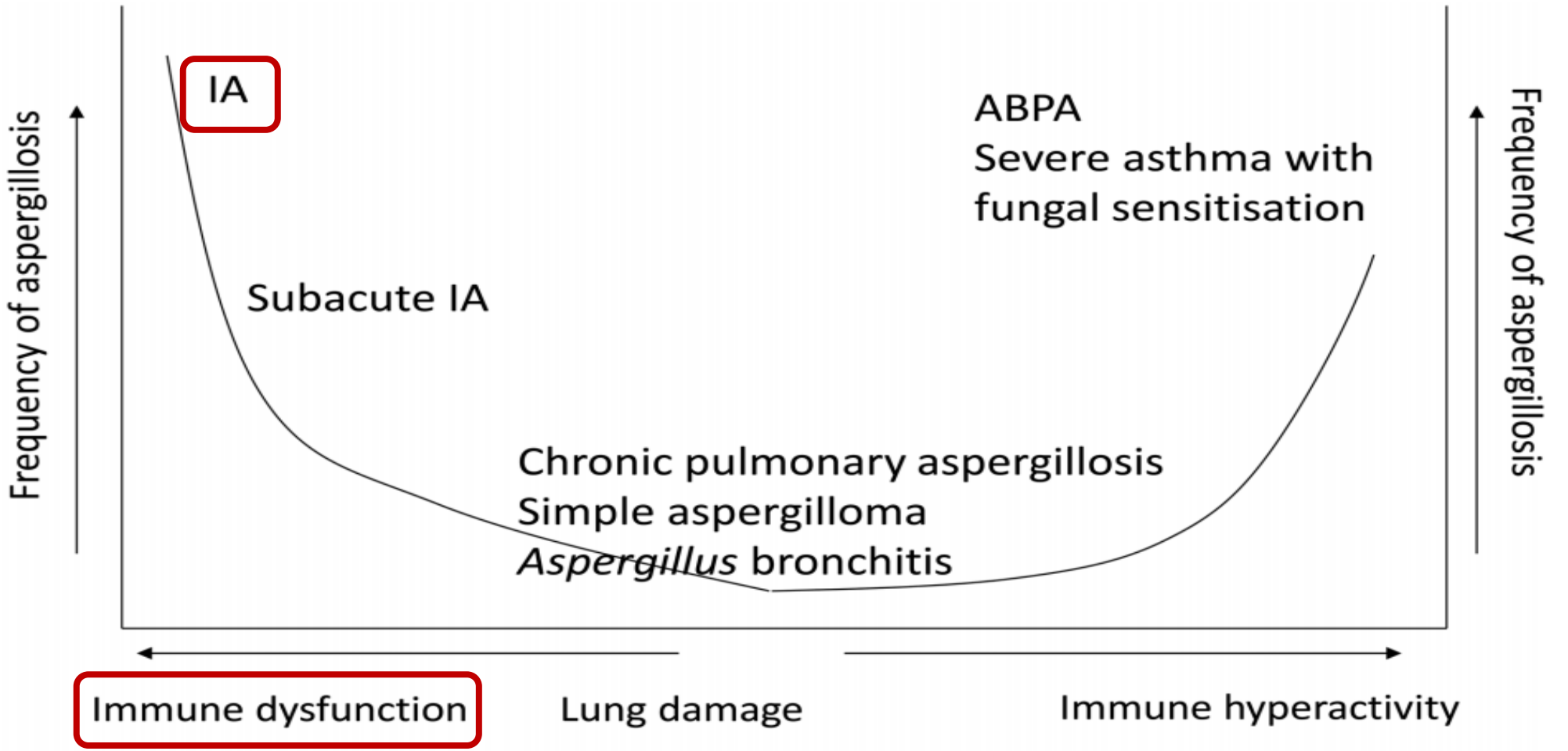


Figure 1 Interaction of *Aspergillus* with host. ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis.

Kosmidis C, et al. Thorax 2015;70:270–277.

İnvazif Pulmoner Aspergilloz (İPA)

- En sık ***Aspergillus fumigatus***, daha nadir *A. flavus*, *A. terreus*, *A. niger*
- İnfeksiyöz konidyaların inhalasyonu
- **İmmunosupresif hastalarda doku invazyonu**
  - Hematolojik kanser tedavisi
  - Hematopoietik kök hücre nakli (HSCT)
  - Solid organ nakli (SOT)

- **Kesin Tanı: Kültür + Histopatolojik inceleme (Dokuda hifalar)**

- Komplikasyon riski nedeniyle biyopsi yapılamayan durumlar

- **Non-invazif yöntemler**: Serum biyobelirteçleri (GM, BDG)
  Balgam ve/veya BAL örneği (boyama, kültür, GM)

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

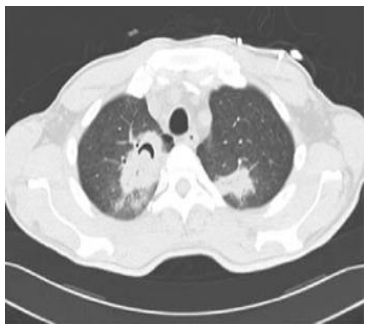
İnvazif Pulmoner Aspergilloz (İPA) - TANI

Klinik bulgular

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

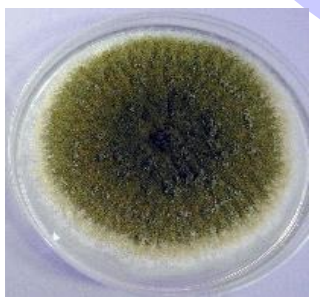


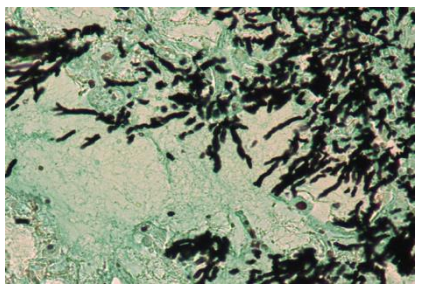
Radyolojik bulgular

TANI

GM Ag

Mikrobiyolojik-Histopatolojik veriler

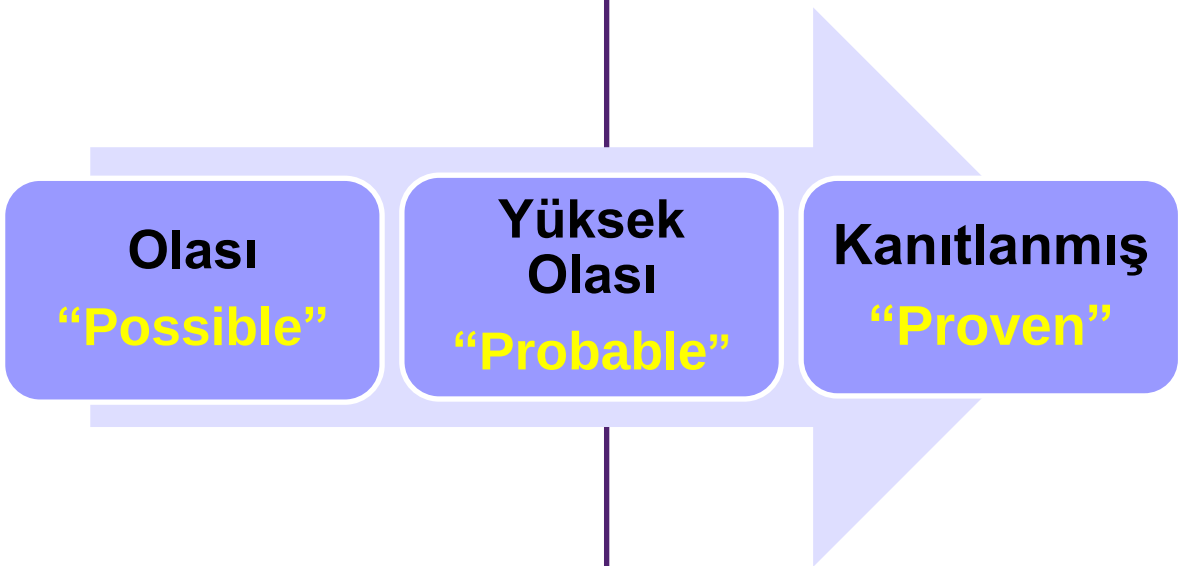




Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

TANI YÖNTEMLERİ

- Solunum örneklerinin direkt incelemesi
- Kültür
- Histopatoloji
- Galaktomannan (GM)
- 1-3 β-D Glukan
- PCR
- Görüntüleme
- Geliştirilmekte olan yöntemler



De Pauw B, et al**. EORTC**. Clin Infect Dis. 2008;46(12):1813.
Ascioglu S, et al. Clin Infect Dis. 2002;34(1):7.

Direkt Mikroskopik İnceleme

- **Kalkoflor beyazı + 10% KOH**
- **45° açıyla dallanan septalı hyalen hifaları** (3-6 mikron)
  - Diğer filamentöz mantarlar *(Scedosporium* spp ve *Fusarium* spp)
- **Duyarlılık:** düşük

- **Gomori Metenamin gümüş boyama - PAS**: sitoloji preparatları

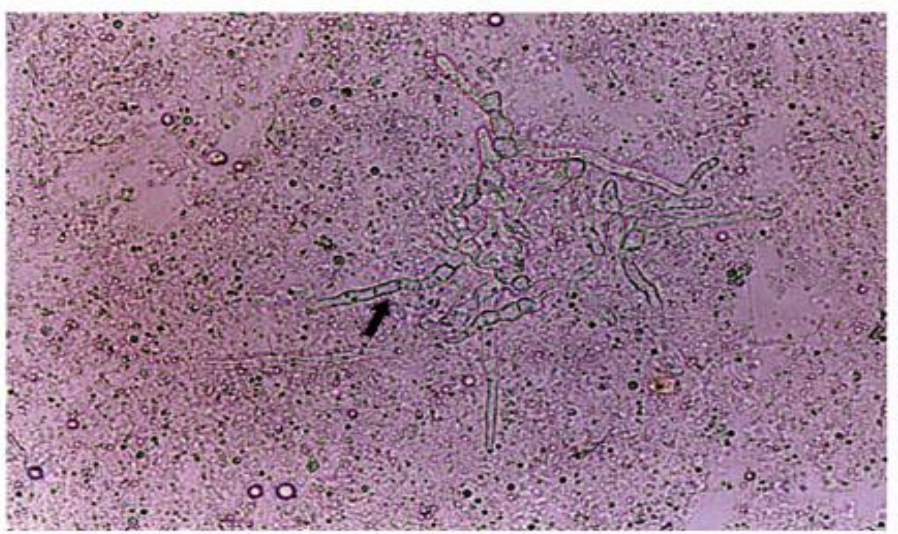
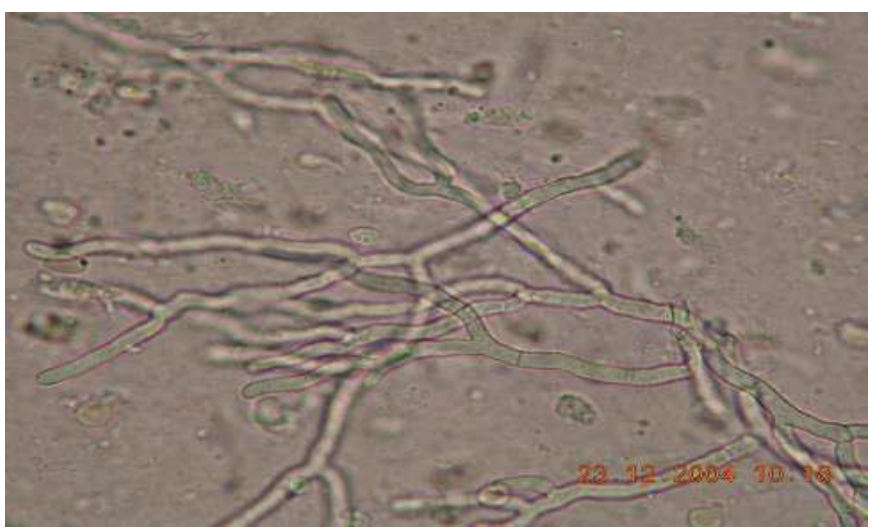


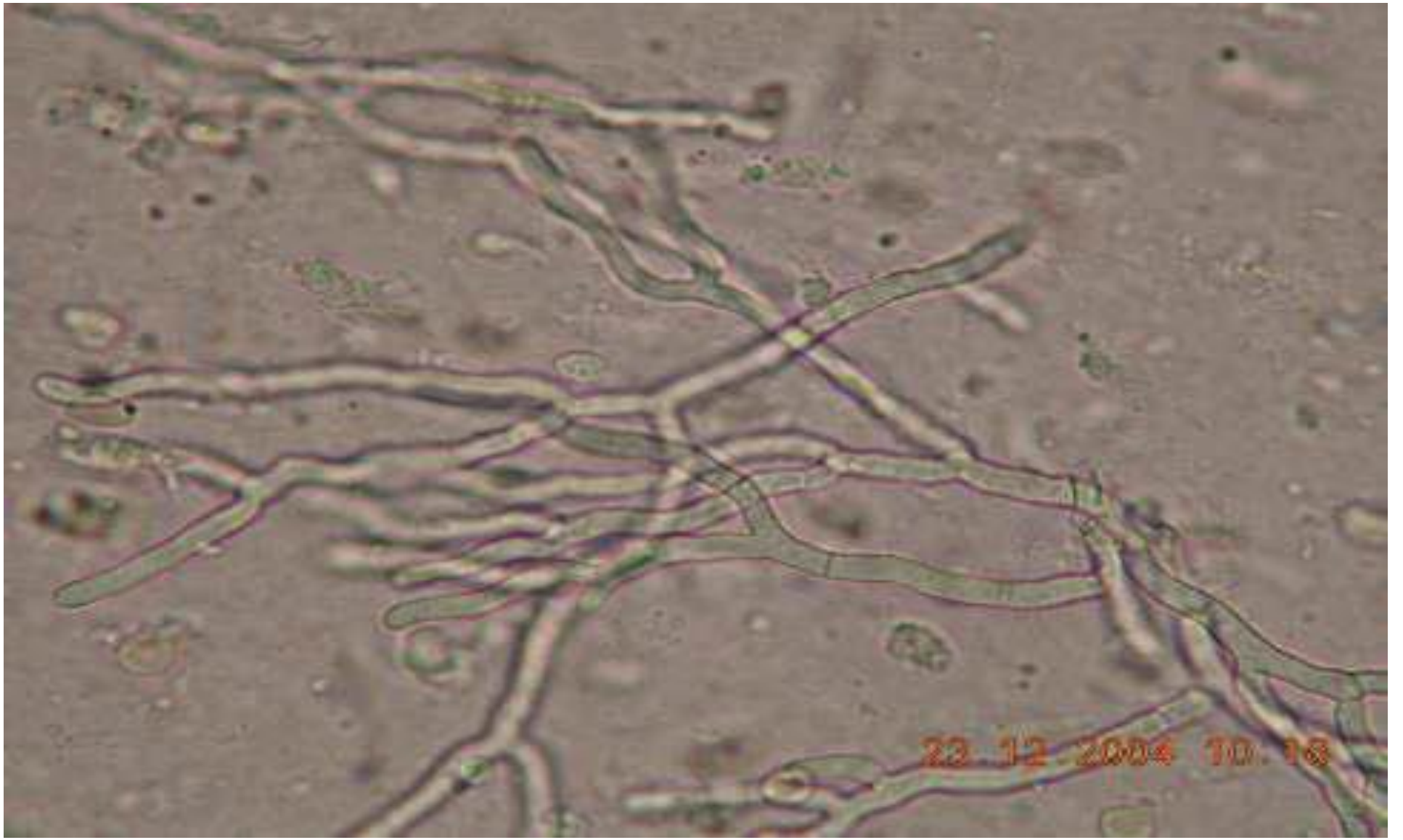
Fig. 2 - Direct mycological examination of the brain abscess material showing septate hyaline hyphae (*arrow*) (X 400).



Schwartz S, et al. Blood. 2005;106(8):2641. Epub 2005 Jul 5.
Pascual A, et al. Clin Infect Dis. 2008;46(2):201.

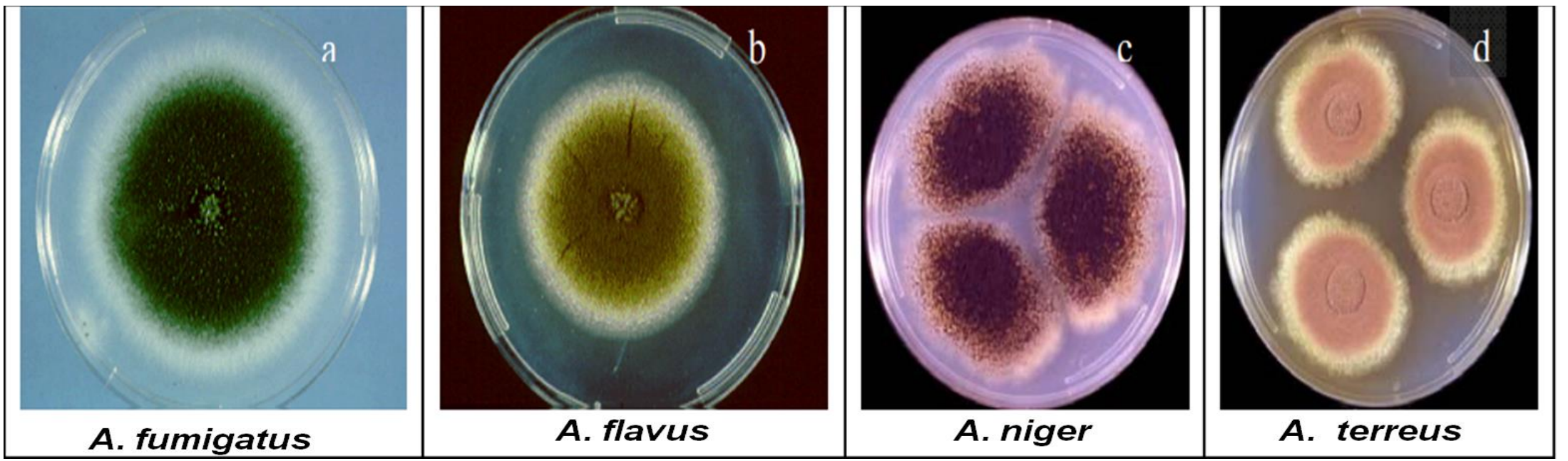
Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

Aspergillus spp - Direkt mikroskopik inceleme



Kültür

- Normalde steril bölgeden örnekte üreme, doku invazyonu
  - **Duyarlılık:** düşük (GM + olan HSCT alıcılarında **%** 25-**50**)
  - **PPV: BAL kültürleri**nde en yüksek (bronkoskopi yapılan hastalarda akciğer infiltrasyonları mevcut)
  - BAL örneği sentrifuj edilmeli



Schwartz S, et al. Blood. 2005;106(8):2641. Epub 2005 Jul 5.
Pascual A, et al. Clin Infect Dis. 2008;46(2):201.

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

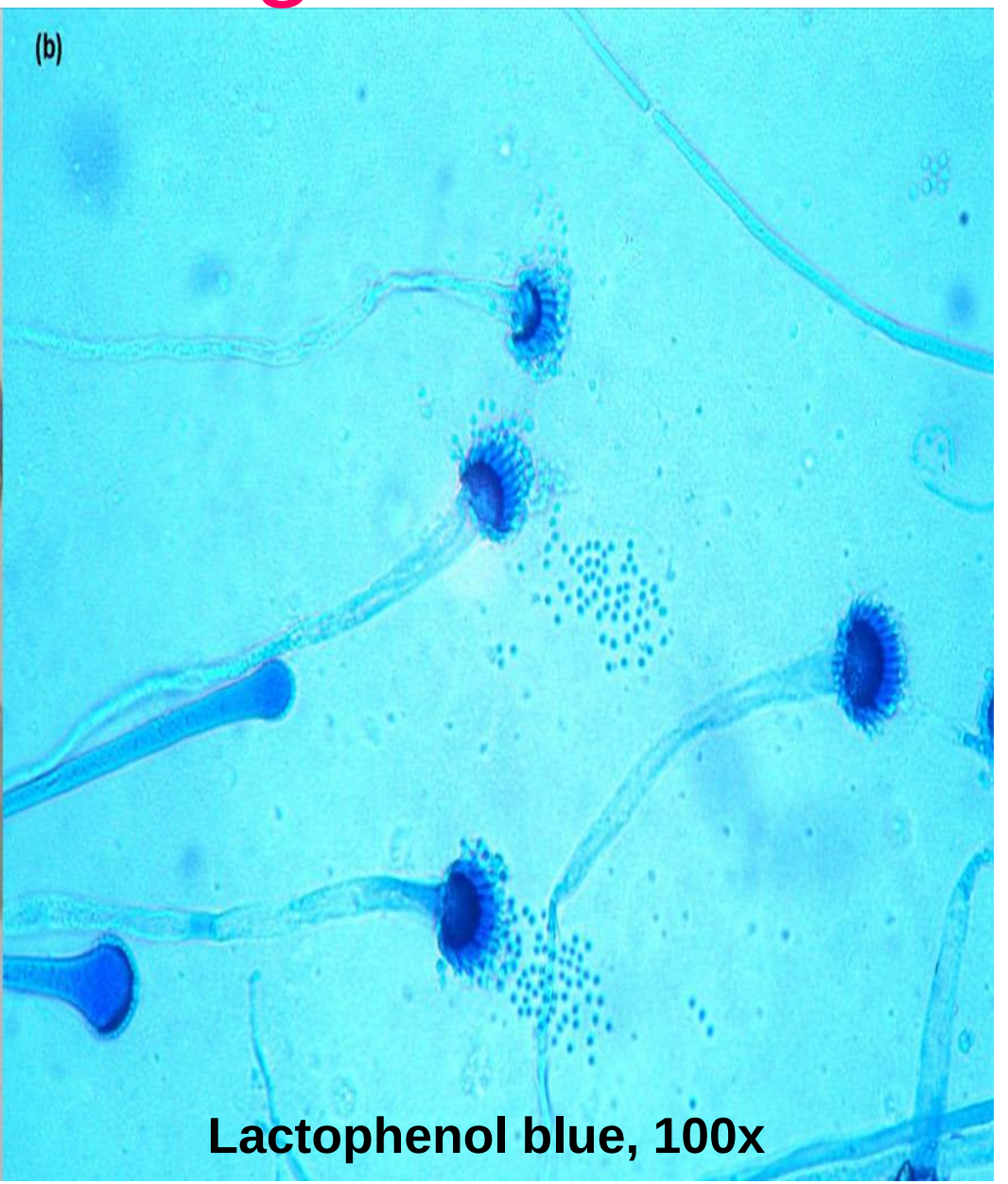
Kültür

- Hızlı üreme: 1-3 günlük inkübasyonda görülebilir.
- Spor içeren yapıları görebilmek için sporulasyon gerekir.
- Yavaş sporulasyon ! : *Aspergillus lentulus*, *Neosartorya udagawae* (invazif infeksiyon)
- **Balgam veya BAL kültürü pozitif prediktif değeri (PPV):**
  - Konak
  - Klinik prezentasyon:
    - HSCT alıcılarında, hematolojik kanser ve nötropenik hastalarda en yüksek (**%72**)
    - SOT, steroid alanlarda: %58
    - HIV: %14
  - BAL'da daha yüksek (%50 duyarlılık; %95 özgüllük)

Howard A, et al. Ann Pharmacother. 2008;42(12):1859. Epub 2008 Nov 18.
Maertens J, et al. Cancer. 2006;107(12):2888.

Kültür – *A.fumigatus*

Sabouraud's agar



Lactophenol blue, 100x

*G. Desoubeaux et al. / Médecine et maladies infectieuses 44 (**2014**) 89–101*

ESCMID: Mikroskopik İnceleme

Table 3
Microscopic examinations

Population	Intention	Intervention	SoR	QoE	Comment
Any	To identify fungal elements in histological sections and stains	Histological examination Gomori's methenamine silver stain Periodic acid–Schiff	A	III	Histopathology is an essential investigation Inability to definitively distinguish other filamentous fungi GMS: removes cellular background; more sensitive to hyphal elements PAS: advantage of counter stain to check cellular detail
Any	To identify fungal elements in histological sections and stains	Fluorescent dyes: Calcofluor white™, Uvitex 2B, Blancophor™	A	II	Not specific to *Aspergillus* but high sensitivity and the micromorphology may provide information on the fungal class (e.g. *Aspergillus*: typically dichotomous and septate, Mucorales: pauci-septate and 90° angle branching, yeast: budding) Rapid turnaround time Broad applicability May be applied to frozen sections, paraffin-embedded tissue
Any	To identify fungal elements in histological sections and stains	Immunohistochemistry Monoclonal antibody WF-AF-1 or EB-A1 *In situ* hybridization	B	II	Have the potential to provide genus- and species-specific data Commercially available monoclonal antibodies WF-AF-1 is specific for *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger* Time consuming and not broadly available
Any	To identify fungal elements in fresh clinical specimens (e.g. BAL)	Application of fluorescent dyes Calcofluor white™ or Uvitex 2B or Blancophor™	A	II	Essential investigation Not specific for *Aspergillus* species High sensitivity Rapid turn-around time Broad applicability No species identification but the micromorphology may provide information on the fungal class (e.g. *Aspergillus*: typically dichotomous and septate, Mucorales: pauci-septate and 90° angle branching, yeast: budding)

Abbreviations: BAL, bronchoalveolar lavage; CNS, central nervous system; GMS, Gomori's methenamine silver stain; HE, haematoxylin-eosin; PAS, Periodi
Quality of evidence; SoR, Strength of recommendation.

Ullmann A.J., et al. Clinical Microbiology and Infection (**2018**), e1ee382.

ESCMID: Kültür ve identifikasyon

Table 5
Culture and *Aspergillus* species identification

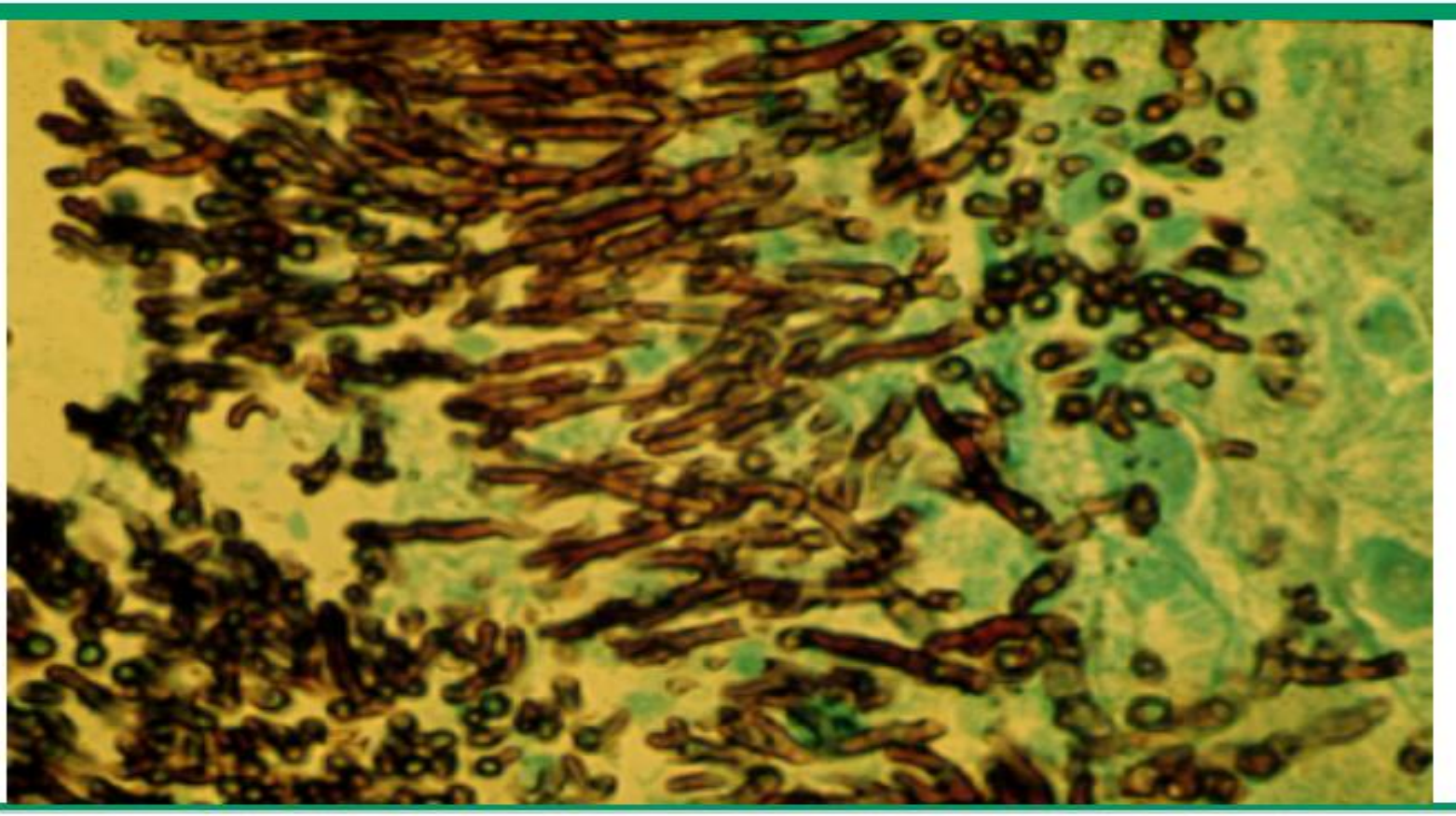
Population	Intention	Intervention	SoR	QoE	Comment
Any	Primary isolation from deep sites samples (e.g. biopsies, blood, CSF)	Culture on SDA, BHI agar, PDA at 30°C and 37°C for 72 h	A	III	Blood inhibits conidiation; BHI can help to recover some isolates; isolation of several colonies or isolation of the same fungus from a repeat specimen enhance significance
	Primary isolation from non-sterile samples, e.g. sputum, respiratory aspirates	Culture on SDA, BHI agar, PDA with gentamicin plus chloramphenicol at 30°C and 37°C for 72 h	A	III	High-volume sputum culture (entire sample) shown to significantly increase recovery; quantitative cultures are not discriminative for infection or colonization
	Identification of species complex	Macroscopic and microscopic examination from primary cultures	A	II	Colony colour, conidium size, shape and septation. Colour of conidia and conidiophore and conidiogenesis (tease or tape mounts are preferred); expertise needed for interpretation
	Identification of species complex (and species identification of *A. fumigatus* specifically)	Culture on identification media at 25–30°C, 37°C and 50°C (2% MEA and Czapek-Dox Agar) and microscopic examination	A	II	Thermotolerance test (growth at 50°C for species confirmation of *A. fumigatus*)
	Identification at species level	MALDI-TOF MS identification	B	II	In-house databases are often used to improve identification rates
	Identification at species level	Sequencing of ITS, β-tubulin and calmodulin	A	III	Not necessary in organisms with typical growth, but in cases of atypical growth
	To study outbreaks	Microsatellite and CSP analysis	C	II	To study outbreaks (which in general may comprise more than one genotype)
			B	II	To study colonization patterns

Abbreviations: BHI, brain–heart infusion; CSF, cerebrospinal fluid; CSP, cell surface protein; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted l ionization time-of-flight mass spectometry identification; MEA, malt extract agar; PDA, potato dextrose agar; QoE, Quality of evidence; SDA, Sabouraud dex Strength of recommendation.

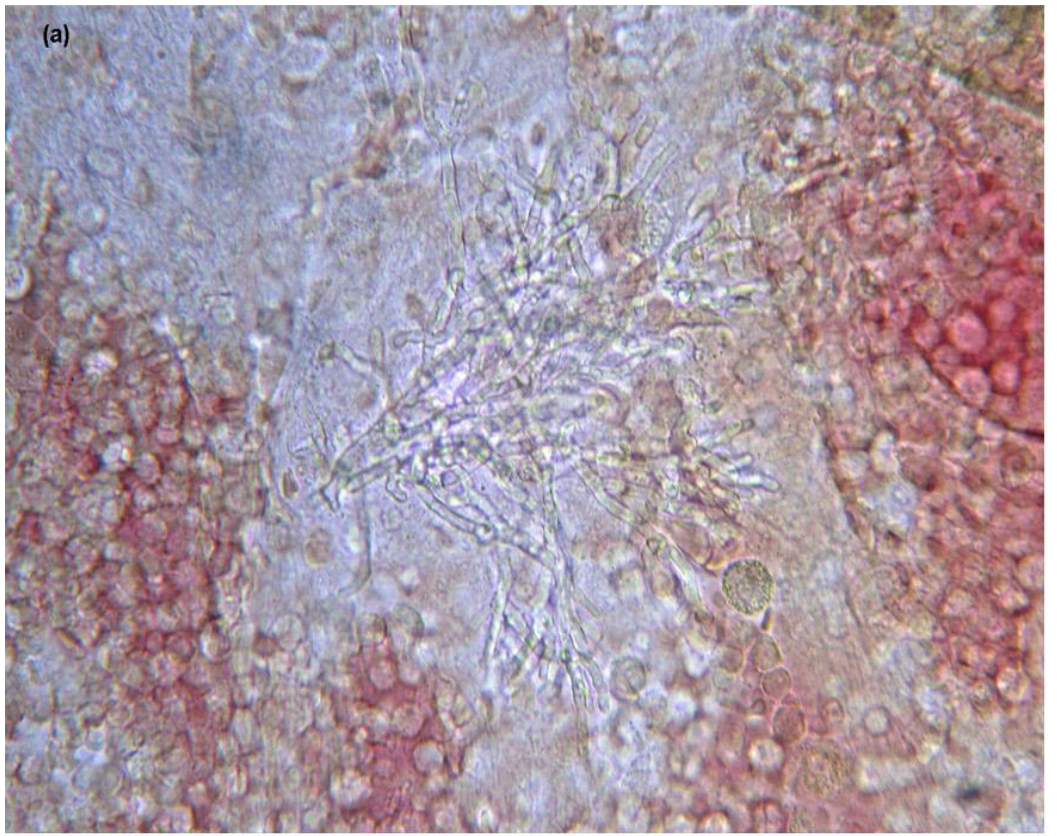
Ullmann A.J., et al. Clinical Microbiology and Infection (**2018**), e1ee382.

Gomori Metenamin gümüş boyama

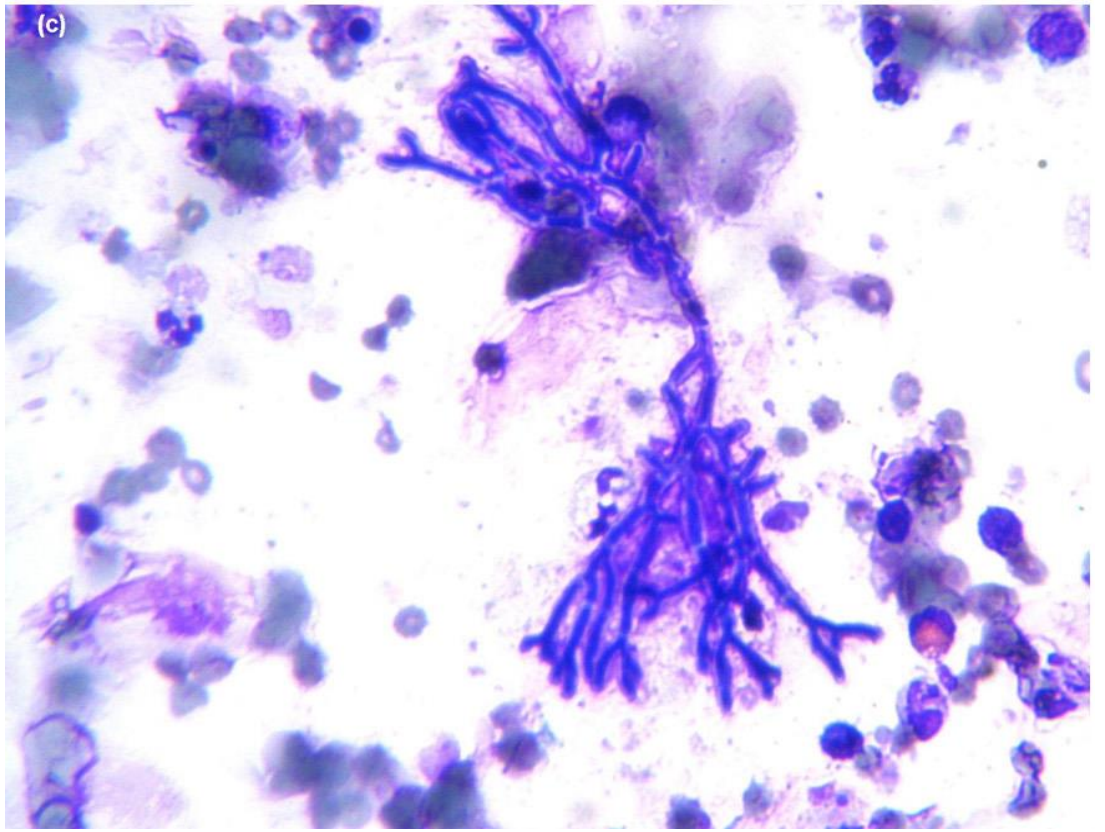
Aspergillus fumigatus



Silver stain of lung tissue (x400) shows septate hyphae with acute angle branching characteristic of *Aspergillus fumigatus*.



Taze preparat direkt inceleme



May-Grünwald-Giemsa

*G. Desoubeaux et al. / Médecine et maladies infectieuses 44 (**2014**) 89–101*

İnvazif Pulmoner Aspergilloz (İPA) - TANI

- **Klinik ve radyolojik** olarak invazif fungal infeksiyonla **uyumlu** bulgular; fakat **serum GM (-)** ve **fungal boyama ve kültürler (-)** ise;
  - **Bronkoskopi – BAL***
  - Mümkünse **akciğer biyopsisi**:
    - Bronkoskopiyle Transbronşiyal biyopsi
    - BT eşliğinde transtorasik iğne biyopsisi
    - Video-aracılı torakoskopik cerrahi (VATS)
- Histopatolojik tanı gerekliliğine hasta bazında karar verilmeli

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

Histopatolojik İnceleme

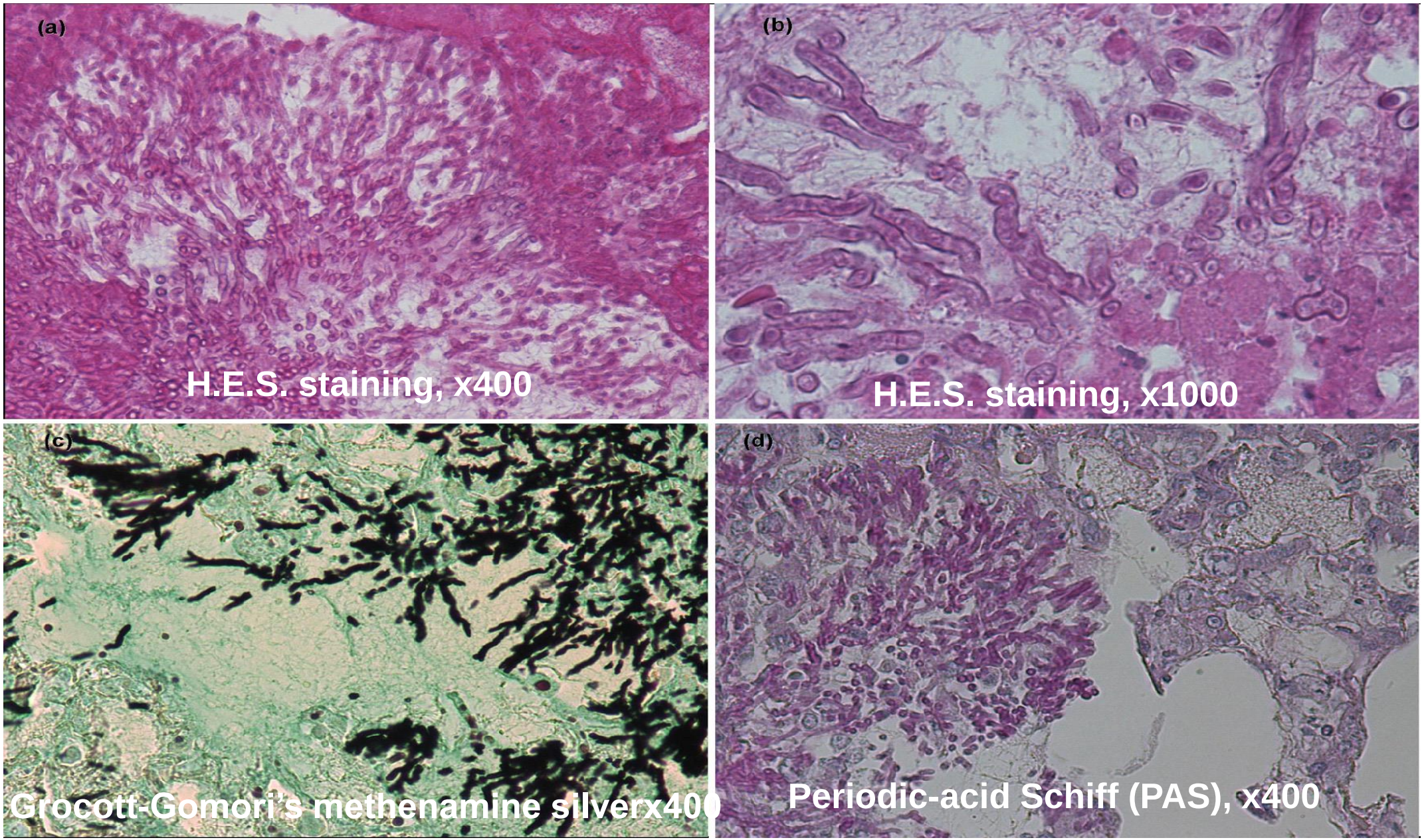
- Histoloji İA tanısında önemli, ancak immun suprese hastada her zaman biyopsi almak mümkün değil

- **Gomori Metenamin gümüş boyama**
- **Periodic acid-Schiff (PAS) boyama**

- ***Scedosporium spp* ve *Fusarium spp***: *Aspergillus spp*'ye benzer görüntü
  - **Kültürde cins ve tür düzeyinde tanımlama**

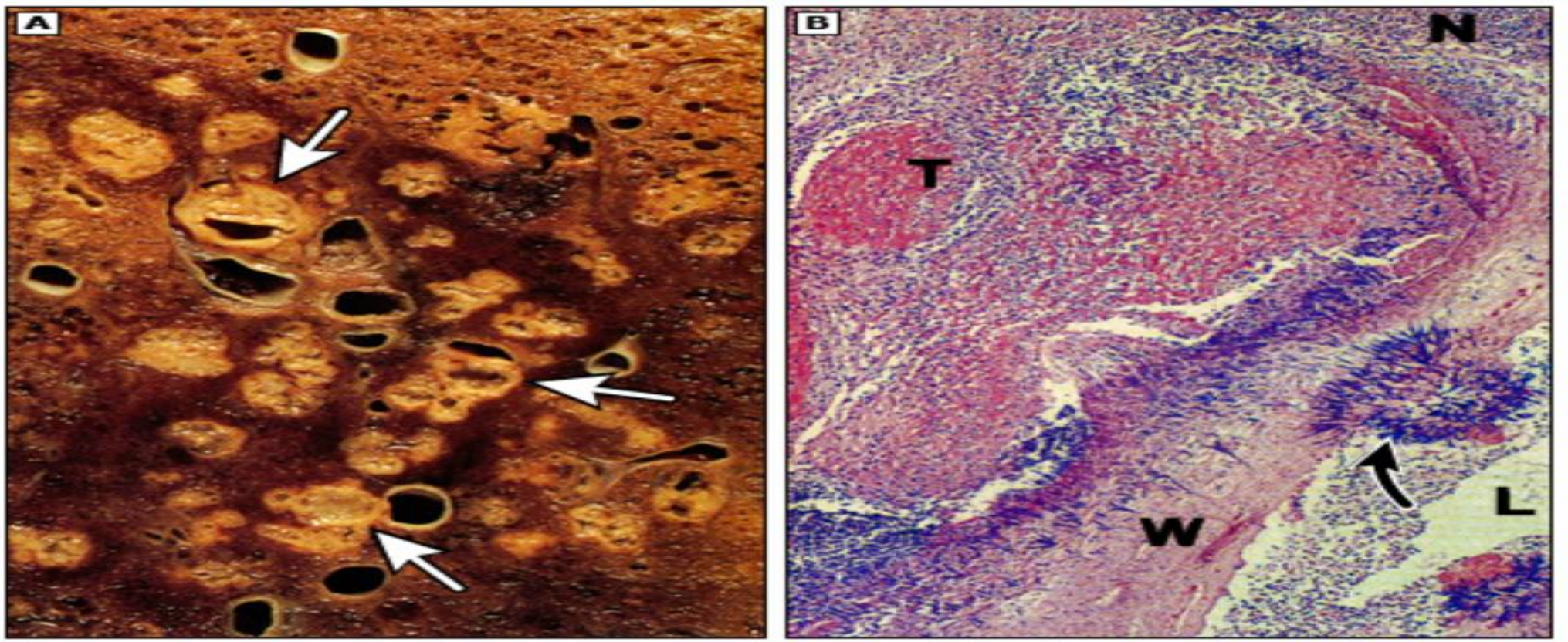
- **Mucorales**: dik açıyla dallanan geniş, septasız hifalar ! (psödoseptasyon)

Histopatolojik İnceleme



*G. Desoubeaux et al. / Médecine et maladies infectieuses 44 (**2014**) 89–101*

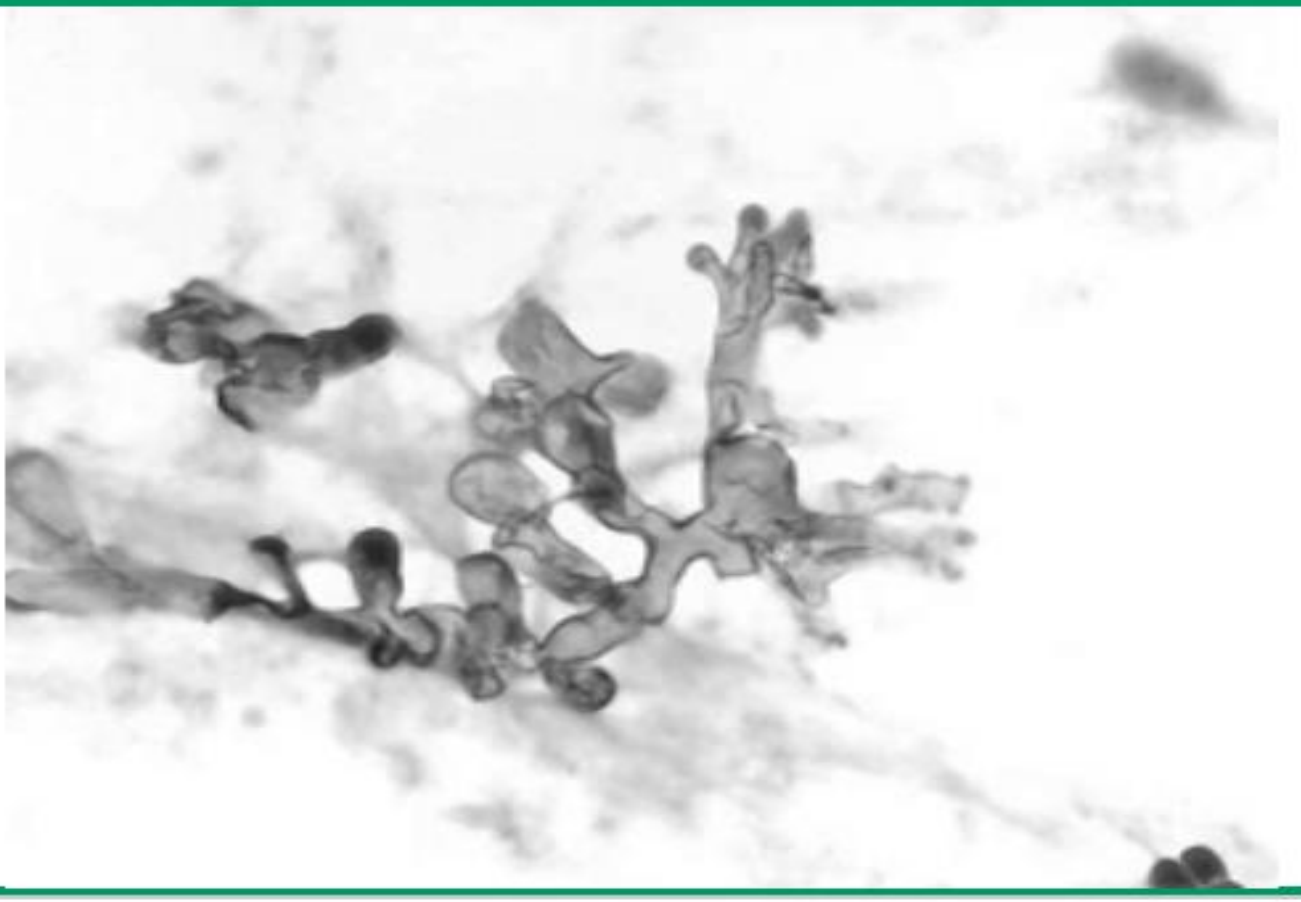
Aspergillus bronchopneumonia histopathology



(Panel A) Magnified view of a slice of lower lobe shows multiple foci of necrosis, some clearly centered on airways (arrows) as indicated by their intimate association with pulmonary arteries. The lung parenchyma adjacent to the necrotic regions is hemorrhagic.
(Panel B) Photomicrograph shows small colonies of *Aspergillus* (arrow) within a bronchial lumen (L) and wall (W). Extension of fungus can also be seen into the adjacent pulmonary artery, which is partly occluded by thrombus (T). An infiltrate of neutrophils (N) is evident in the adjacent lung.

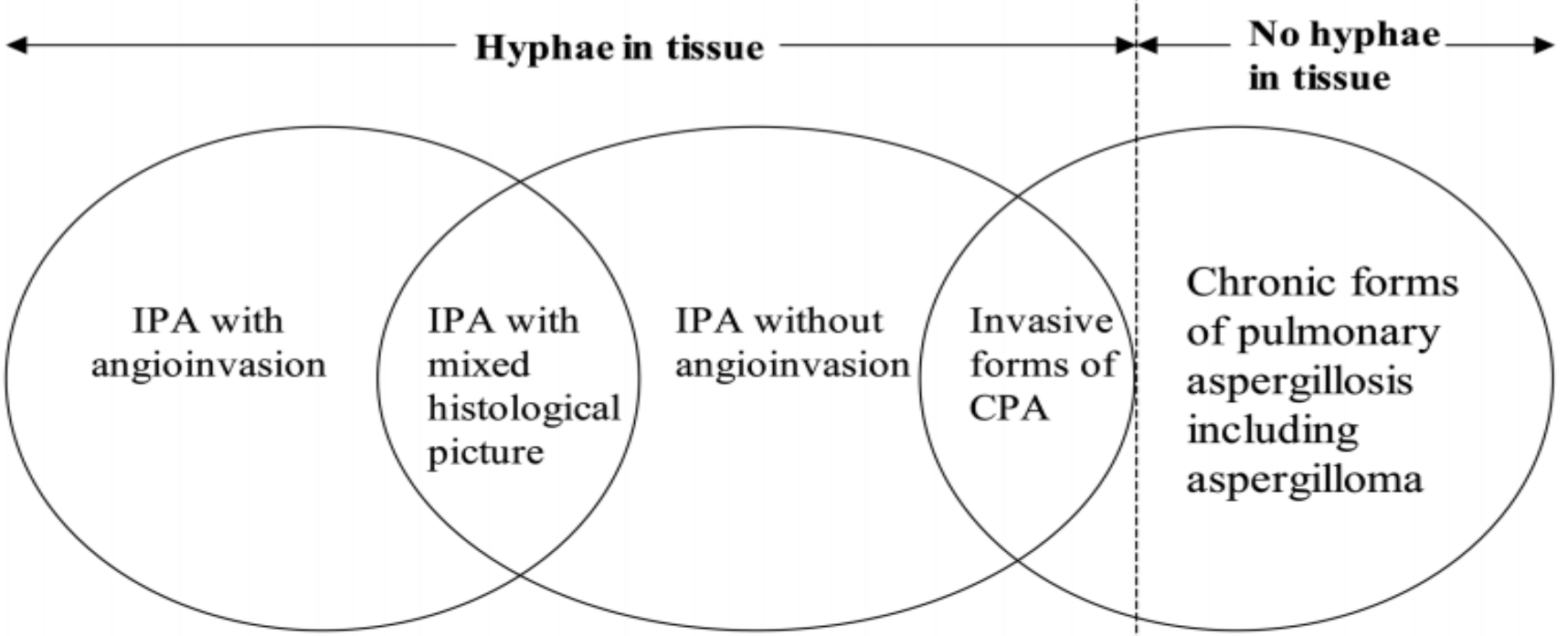
Uptodate

Mucorales hyphae



Fine needle aspiration of right lower lobe of lung showing aseptate hyphae (Papanicolaou stain, x400).

İPA



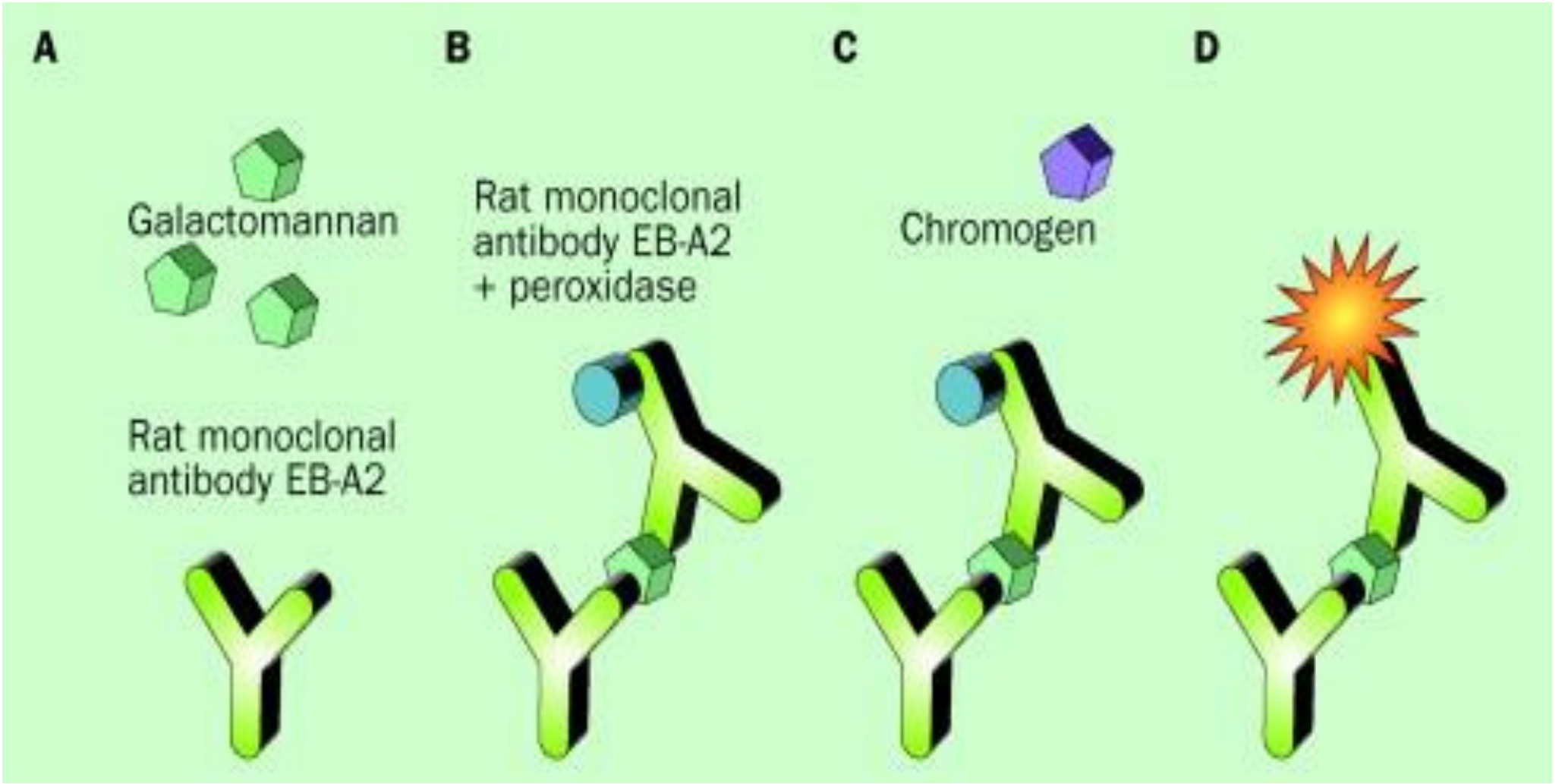
Pathology	Angioinvasion, coagulative necrosis, haemorrhagic infarction	No angioinvasion, pyogranulomatous inflammation, inflammatory necrosis	No angioinvasion, hyphae confined to pre-existing lung cavity
Host	Prolonged and profound neutropenia	Non-neutropenic with CGD, corticosteroid therapy, HIV/AIDS, non-neutropenic HSCT recipients, GVHD	Pre-existing structural lung disease, minor immunological defects
Time-course	Days-weeks	Weeks-months	Months-years

Kosmidis C, et al. Thorax 2015;70:270–277.

GALAKTOMANNAN (GM)

- *Aspergillus spp* hücre duvarında polisakkarit
- **EIA**: EB-A2 monoklonal antikoru kullanılır.
- **Serum ve BAL'da GM**: FDA onaylı
- **IFI'yi dışlamada kullanılır (NPV yüksek), PPV düşük**
- **Duyarlılık:** (~% 70)
- **Özgüllük:** (~% 90)
- Klinik uyumluysa İPA tanısı için yeterli kanıt
- **ODI (optik dansite indeksi):** kontrol "cut-off" **OD'ne rölatif oranı**
- Avrupa'da: yüksek eşik değer: 1 - 1.5 ODI
- Düşük eşik değer: 0.5 - 0.7→ daha iyi performans
- **FDA: ≥ 0.5 → pozitif sonuç** (küflere etkili AF almayanlarda duyarlılık yüksek)

GALAKTOMANNAN (GM)



Although once described as being *Aspergillus* specific, we now know that galactofuranose is present in other fungi and certain other substances:

Fusarium* spp, *Penicillium* spp , *Histoplasma capsulatum

GALAKTOMANNAN (GM)

- **OD index cutoff : 0.5**

  sensitivite: %30-100, spesifisite: >%75

  - BAL sıvısında GM duyarlılık >%70

- **Hematolojik malignite**
- **HSCT alıcıları**

} **Test performansı daha iyi**

- **SOT alıcılarında sınırlı performans**
- **PPD: <%50, NPD: >%90**
- **Tedaviye yanıt – prognoz**

Leeflang MM,et al. Cochrane Database Syst Rev. 2015
Pfeiffer CD, Fine JP, Safdar N SOClin Infect Dis. 2006;42(10):1417.

GM - Uyarılar !

- **Küflere etkili antifungal tedavi** alanlarda **GM duyarlılığı düşük**
- Mevcut **piperacilin-tazobactam** preparatlarıyla **nadiren yanlış pozitiflik** oranı

- **IV amoksisilin-klavulonat**

- **Antijenik benzerlik** (galactofuranose içeren PS) → **X reaksiyon** *:*
  - *Fusarium* spp, *Penicillium* spp , *Histoplasma capsulatum*

- HSCT sonrası ilk 100 günde **KT/GVHD'ye bağlı GIS mukoziti** olanlarda **yanlış pozitiflik** (besin ve bakterilerdeki GM translokasyonu)

Mikulska M, et al. Bacigalupo A, Viscoli C SOJ Antimicrob Chemother. 2012 Jul;67(7):1746-8.
Vergidis P, et al. J Clin Microbiol. 2014 Jun;52(6):2199-201.

GM - Uyarılar !

- **Besinlerin** *Aspergillus spp* ile **kontaminasyonu** sonucu yanlış pozitiflik
- **BAL için kullanılan sıvıda kontaminasyon**
- Bazı **kan ürünü torbaları**ndan yanlış pozitiflik (Fresenius Kabi, Germany)
- **IVIG alanlarda** yanlış pozitiflik
- **Çocuklarda** bazen yanlış pozitiflik ?
- **AC transplant alıcılarında kolonizasyon:** yanlış pozitiflik

Mikulska M, et al. Bacigalupo A, Viscoli C SOJ Antimicrob Chemother. 2012 Jul;67(7):1746-8.
Vergidis P, et al. J Clin Microbiol. 2014 Jun;52(6):2199-201.

ESCMID: Kan örneklerinde GM Testi

Table 6
Galactomannan testing in blood samples

Population	Intention	Intervention	SoR	QoE	Comment
Patients with prolonged neutropenia or allogeneic stem cell transplantation recipients **not on mould-active prophylaxis**	Prospective screening for IA	GM in blood[a] Draw samples every 3–4 days	A C	I III	Highest test accuracy requiring two consecutive samples with an ODI ≥0.5 or retesting the same sample Prospective monitoring should be combined with HRCT and clinical evaluation
Patients with prolonged neutropenic or allogeneic stem cell transplantation recipients **on mould active prophylaxis**	Prospective screening for IA	GM in blood[a]	D	II	Low prevalence of IA in this setting with consequently low PPV of blood GM test Prophylaxis may have a negative impact on sensitivity of the test or the low yield may be due to decreased incidence of IA
Patients with a haematological malignancy	To diagnose IA	GM in blood[a]			Significantly lower sensitivity in non-neutropenic patients
• Neutropenic patients			A	II	
• Non-neutropenic patients			B	II	
ICU patients	To diagnose IA	GM in blood[a]	C	II	Better performance in neutropenic than in non-neutropenic patients
Solid organ recipients	To diagnose IA	GM in blood[a]	C	II	Low sensitivity, good specificity Most data for lung SOT
Any other patient	To diagnose IA	GM in blood[a]	C	II	Piperacillin/tazobactam may no longer be responsible for false-positive results according to recent studies Cross-reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis) False-positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion
Cancer patients	To monitor treatment	GM in blood[a]	A	II	

Abbreviations: GM, galactomannan; IA, invasive aspergillosis; ICU, intensive care unit; ODI, optical density index; PPV, positive predictive value; QoE, Qu
Strength of recommendation; SOT, solid organ transplantation.
[a] Serum or plasma.

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

ESCMID: Kan-dışı örneklerde GM Testi

Galactomannan testing in samples other than blood

Population	Intention	Intervention	SoR	QoE	Comment
Any	To diagnose pulmonary IA	To apply GM test on BAL fluid	A	II	GM in BAL is a good tool to diagnose, optimal cut-off to positivity 0.5 to 1.0
Any	To diagnose cerebral IA	To apply GM test on cerebrospinal fluid	B	II	No validated cut-off
Any	To detect GM in tissue	To apply GM test on lung biopsies	B	II	Using a cut-off 0.5 resulted in a sensitivity of 90 % and a specificity of 95%; specimens need to be sliced, precondition for doing so is that sufficient material is available; dilution in isotonic saline

Abbreviations: BAL, bronchoalveolar lavage; GM, galactomannan; IA, invasive aspergillosis; QoE, Quality of evidence; SoR, Strength of recommendation.

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

1-3-β-D Glukan

- Mantarların hücre duvarı bileşeni
- **Panfungal Test:** ***Aspergillus*** *spp* için özgül değil, ***Candida*** *spp,* ***Pneumocystis jirovecii*** ’de +
- **Kriptokok ve zigomiçetleri dışlar.**
- **Sonuçlar:**
  - negatif (<60 pg/mL)
  - indetermine (60-79 pg/mL)
  - pozitif (>80 pg/mL)

- Sensitivite: **%50-77**, Spesifisite: **%85-99**
- **Negatif prediktif değeri (NPV): çok iyi**
- Tarama ile klinik bulgulardan önce İFİ tanısı ???

Lamoth F, et al. Clin Infect Dis. 2012;54(5):633.
Kawazu M, et al. J Clin Microbiol. 2004;42(6):2733.

1-3-β-D Glukan - Uyarılar!

- **Yanlış pozitiflik:**
  - Selüloz membranlarla hemodiyaliz
  - IVIG
  - Albumin
  - Selülöz filtrelerin IV uygulamada kullanımı
  - Seröz yüzeylere gazlı bez teması
  - IV amoksisilin-klavulonat
  - β-glukan içeren bazı bakterilerle infeksiyon(*Pseudomonas aeruginosa)*

ESCMID: β-D-GlukanTesti

Table 8
β-D-glucan assays

Population	Intention	Intervention	SoR	QoE	Comment
Mixed population: adult ICU, haematological disorders, SOT	To diagnose IFD	Diagnostic assay	C	II	Five different assays Overall sensitivity of 77% and specificity of 85% Specificity limits its value in this setting
		Screening assays	C	II	Two or more consecutive samples: sensitivity: 65%; specificity: 93% Studies included once to thrice weekly. Varies with assay and cut-off: Wako assay sensitivity: 40%–97%, specificity: 51%–99%
Adult haematological malignancy and HSCT	To diagnose IFD	Diagnostic assay	C	II	Overall sensitivity: 50%–70%, specificity: 91%–99%
ICU—mixed adult immunocompromised patients (haematology, SOT, cancer, immunosuppressive therapy, liver failure, HIV)	To diagnose IA	Diagnostic assay	C	II	Overall sensitivity: 78%–85%, specificity: 36%–75%, NPV: 85%–92% Specificity increased at higher cut-off values
ICU—mixed adult population: SOT, liver failure, immunosuppressed		Screening assays	C	III	Sensitivity: 91%, specificity: 58%, PPV: 25%, NPV: 98%. Positive mean of 5.6 days before positive mould culture High false-positive rate in early ICU admission
Adult haematological malignancy and HSCT	To diagnose IA	Diagnostic assay	C	II	Overall sensitivity: 57%–76%, specificity: 95%–97%
		Screening assays	C	II	Overall sensitivity: 46%, specificity: 97% Confirmation with GM increases specificity Data suggest BDG is unsuitable for ruling out diagnosis of IA

Abbreviations: BDG, β-D-glucan test; GM, galactomannan; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis; ICU, intensive
fungal disease; NPV, negative predictive value; PPV, positive predictive value; QoE, Quality of evidence; SoR, Strength of recommendation; SOT, sol

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

PCR

- Türe spesifik, sensitif, ancak **çapraz kontaminasyon riski** !
- Real-time PCR: **standardize değil**
- **Duyarlılık ~%85 , özgüllük ~ %75**

- **Galaktomannan haftada 2 kez + PCR + BT** :
  Kanıtlanmış/ yüksek olası İFİ için **PPV %99.6**
  - **Duyarlılık %98 , özgüllük: %95**

- **Multipl test kombinasyonu**, tanısal strateji ile IA dışlanabilir ya da doğrulanabilir.

- PCR kullanıldığında **sonuçlar diğer tanısal testler ve klinikle birlikte değerlendirilmelidir**.

S. Arikan Akdagli, Turkish J Hematol 2014; 31: 342.
White PL, et al. J Clin Microbiol 2016 Apr;54(4):960-6
Barnes RA, et al. J Infect. 2013 Sep;67(3):206-14.

Geliştirilmekte olan yöntemler

- **Lateral flow device (LFD) :** Monoclonal JF5 antikoru kullanarak aktif çoğalan *Aspergillus* spp'nin mannoproteinini saptar. Ucuz, hızlı, özel ekipman gerektirmiyor. (Serum ve BAL örnekleri)
- **Thermal desorption-gas chromatography/ mass spectrometry:** İnsan nefesinde sekonder metabolitleri saptar. "Proven or probable IA" da duyarlılık ve özgüllük yüksek
- **Kombine testler** (serum GM, serum/tam kan PCR, 1-3-β-D Glukan, LFD…)
- **Fluorescent in situ hybridization (FISH)**
- **Immuno-PET / MRI**
- **Presipitin antikorları** (sadece küf mantarlarına allerji tanısı için)

Lateral flow device (LFD)

LFDs for Aspergillus immunoglobulin using unspecified capture antigens in precipitin-positive sera from patients with chronic pulmonary aspergillosis and from precipitin-negative patients (controls).

The upper band is the device control band, and the lower band is the test band

Richardson M, et al.Current Fungal Infection Reports (**2018**) 12:127–136

Thermal desorption-gas chromatography/ mass spectrometry

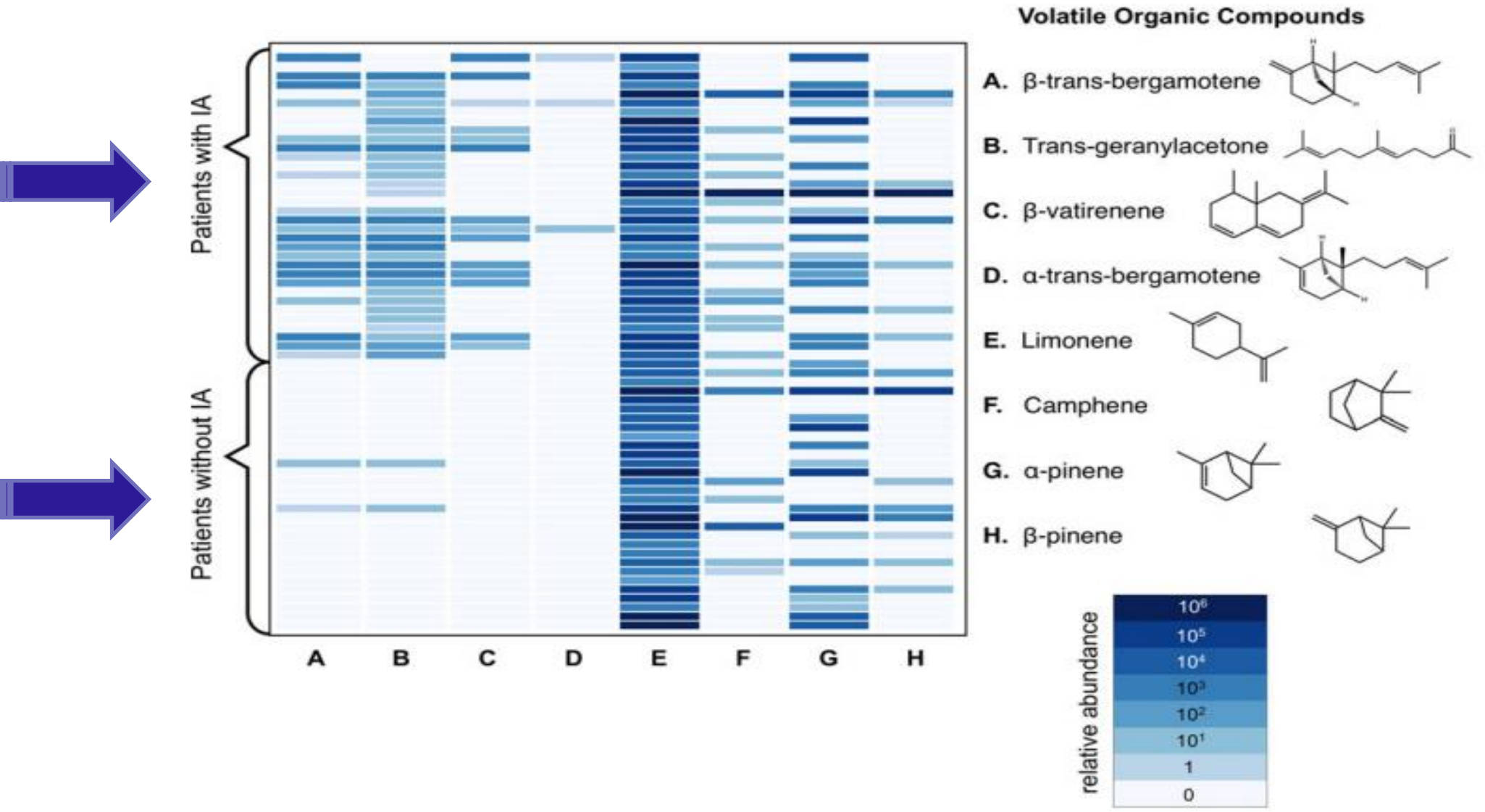


Figure 2. Relative abundance of *Aspergillus* terpene metabolites in breath samples. This heatmap shows the average integrated area of terpene metabolites (columns A–H) in the breath of 64 patients with and without invasive aspergillosis (IA).

Koo S, et al.Breath Diagnosis of Aspergillosis, CID **2014**:59

FISH

Fluorescent in situ hybridization

Cins ve tür düzeyinde tanımlama

(60–90 min)

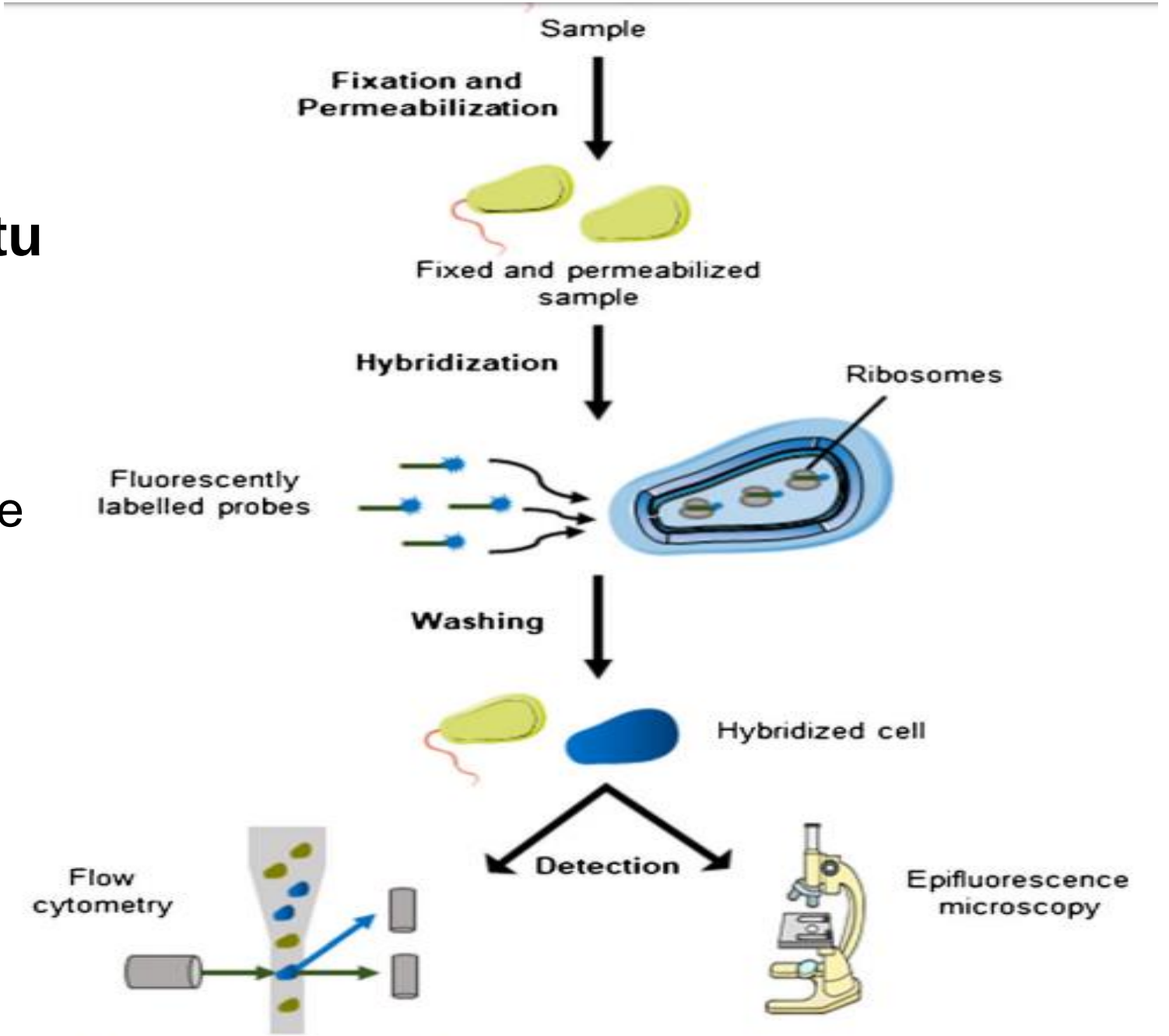


Fig. 1 Main steps of the FISH method

Moura, S., et al. European Journal of Clinical Microbiology & Infectious Diseases (2018)

GÖRÜNTÜLEME YÖNTEMLERİ

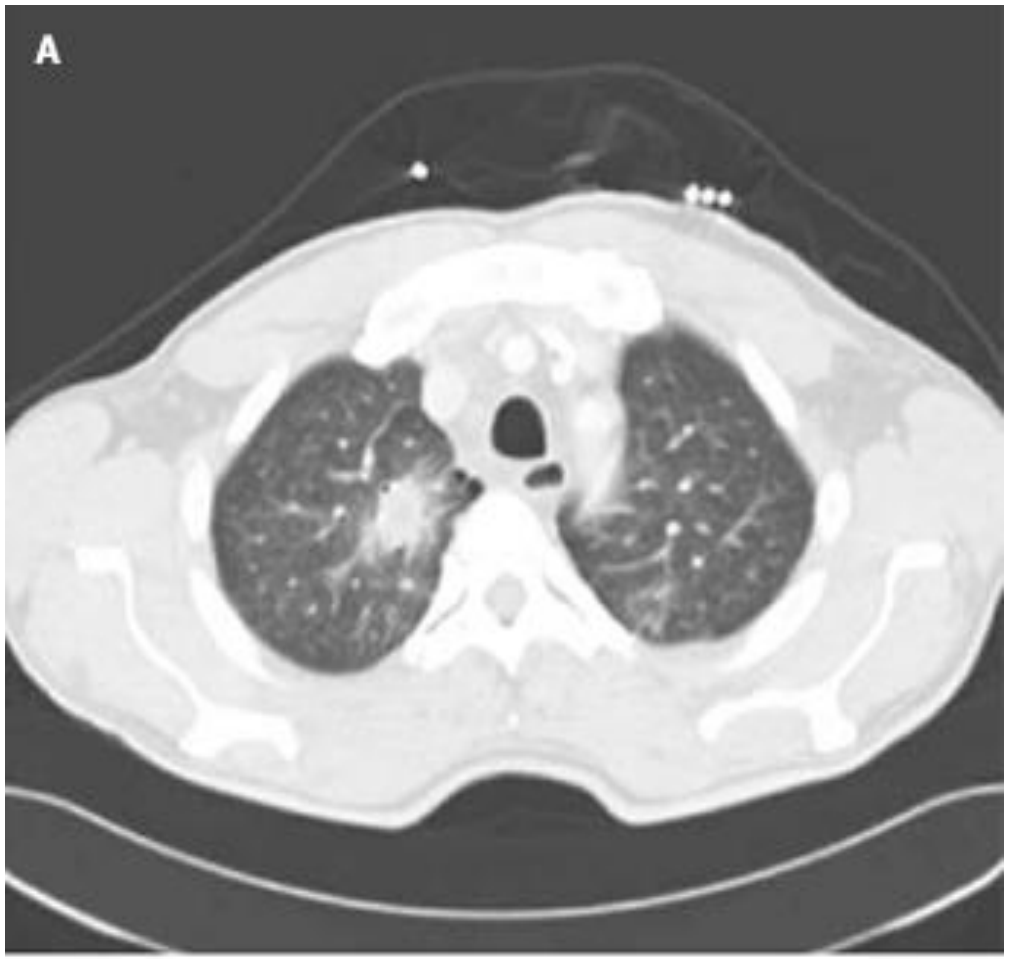
- **İnce kesitli BT, spiral BT, HRCT**
- "ALARA: As Low As Reasonably Achievable"

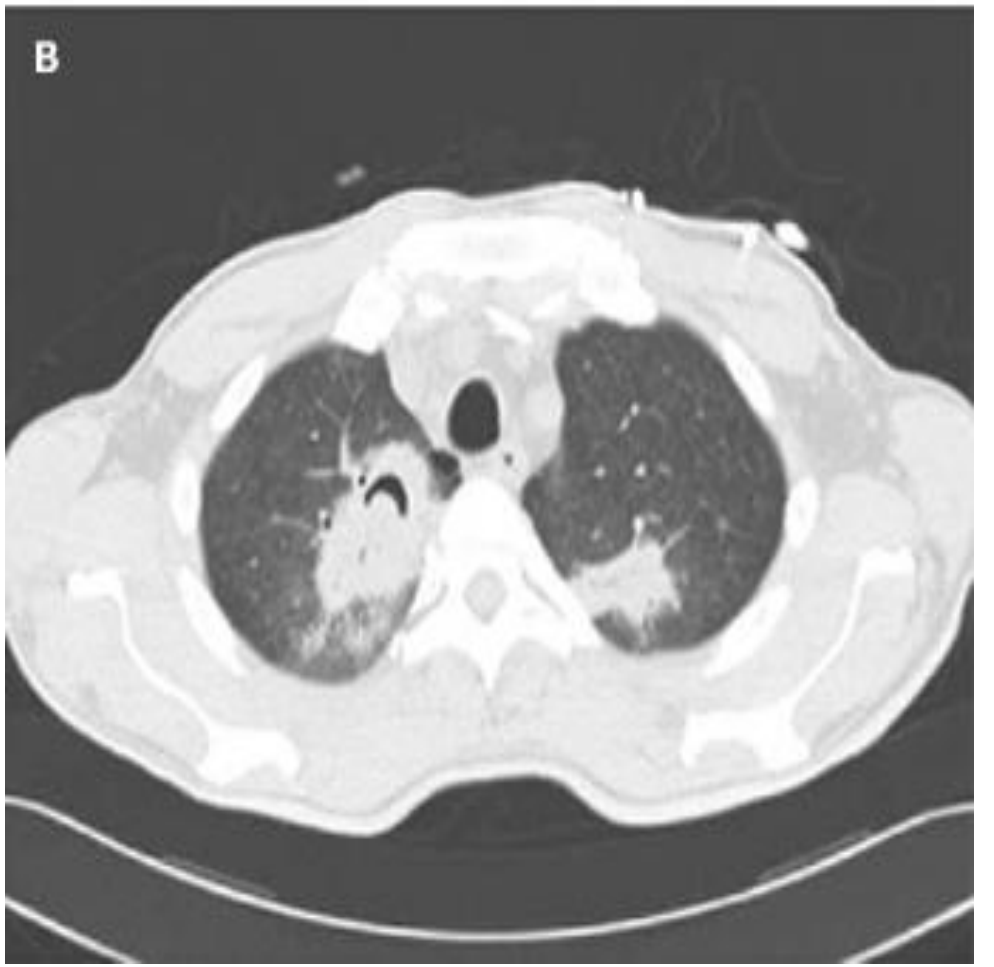
BT bulguları:

- **Halo belirtisi:** makronodül >1 cm etrafında buzlu cam (anjiyo-invazyon)
  - erken bulgu, duyarlı ancak özgül değil
- **"Air crescent" (hava hilal)** bulgusu geç dönemde anjiyo-invazif aspergillozu tanımlar, erken tanıda yararlı
  - plevra tabanlı kama şeklinde konsolidasyon
  - alveoler konsolidasyon
  - SOT alıcılarında kitle
  - Bronkoinvazif formlar: tomurcuklanan ağaç görüntüsü

- Hemoptizi varsa pulmoner BT anjiyografi

BT- IPA





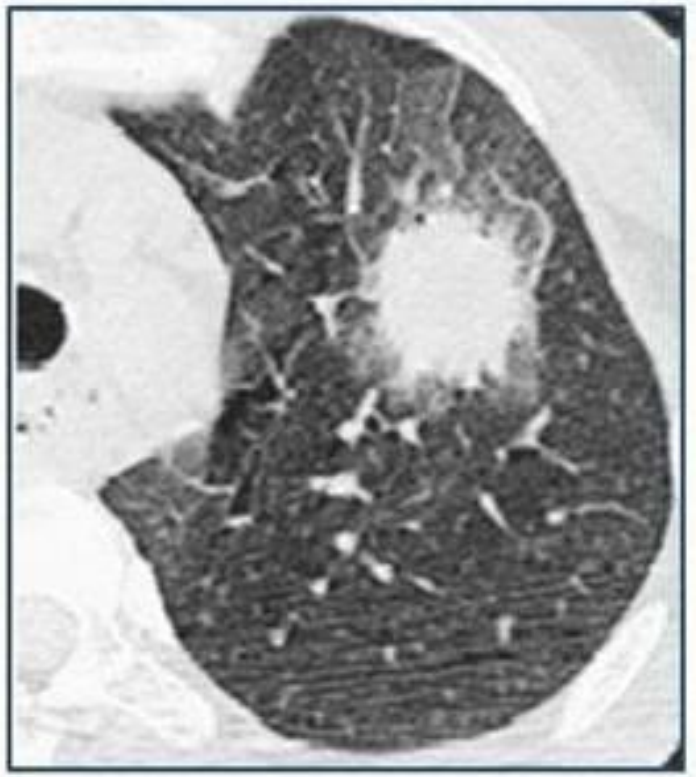
Halo (Ayla) belirtisi

Hava-hilal (Ayça) belirtisi

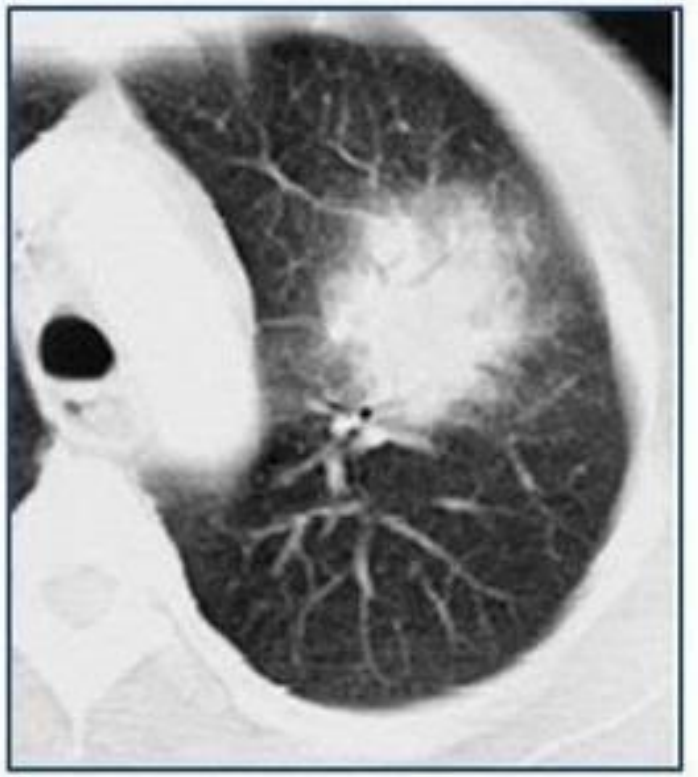
Pogano L et al. Blood Reviews 2010
Sherif R et al. Curr Opin Pulm Med 2010

Akut IPA

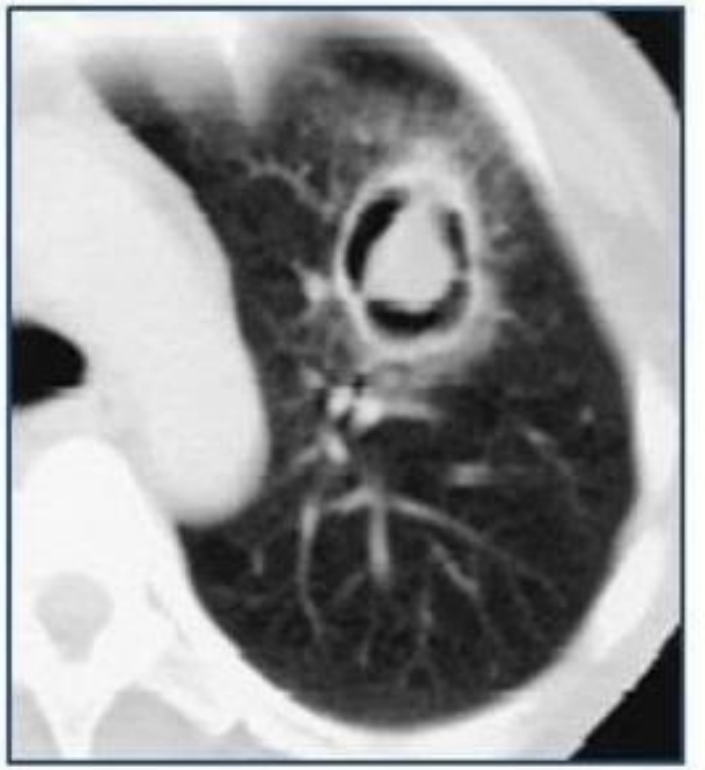
Sequential high-resolution CTs in 25 patients with neutropenia and IPA at diagnosis: median number of lesions=2, bilateral in 48%



Baseline: halo



Day 4: ↑size, ↓halo



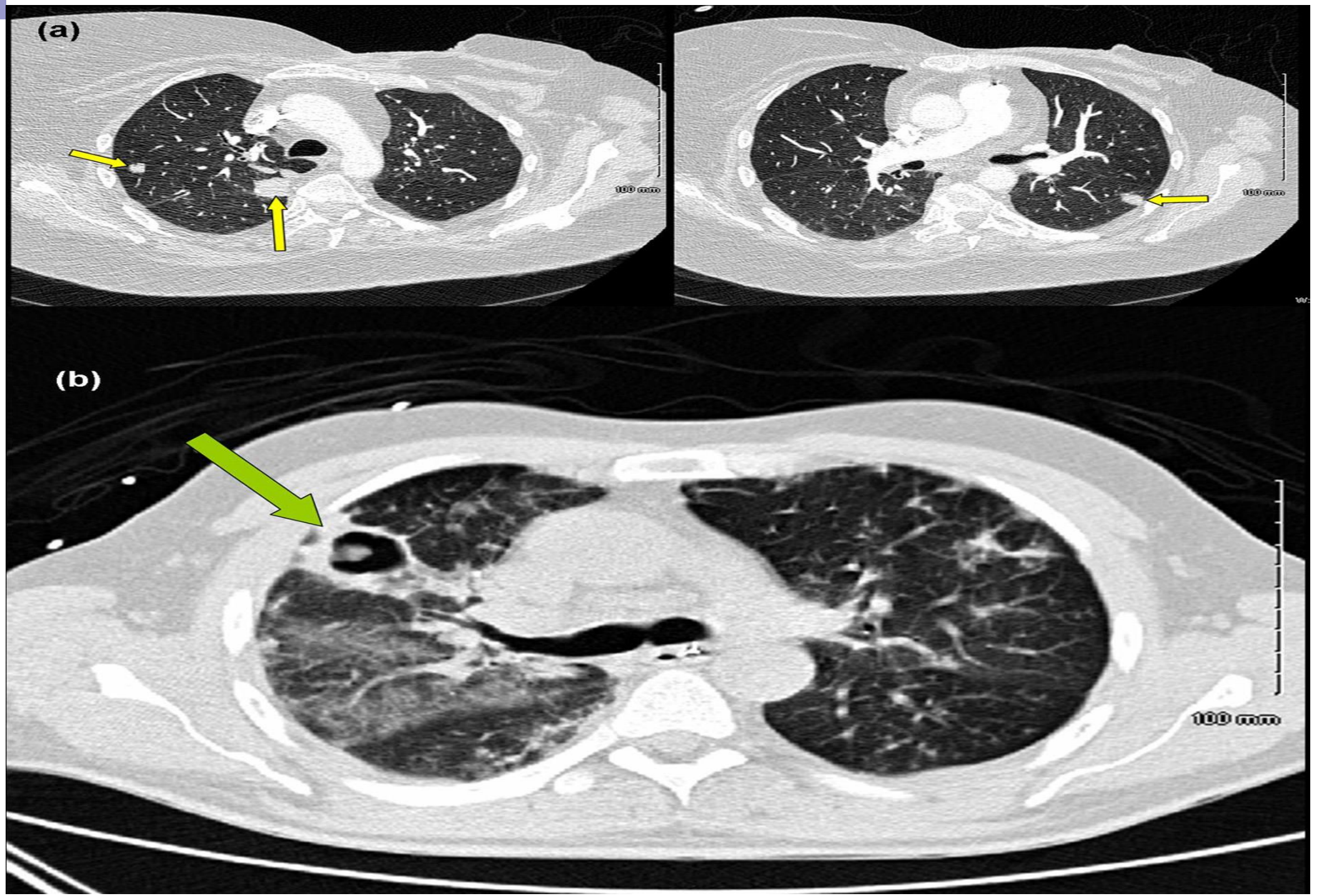
Day 7: air crescent

Halo transitory: <5 days; increased volume for 1 week → stabilization → air crescent

IPA=invasive pulmonary aspergillosis.

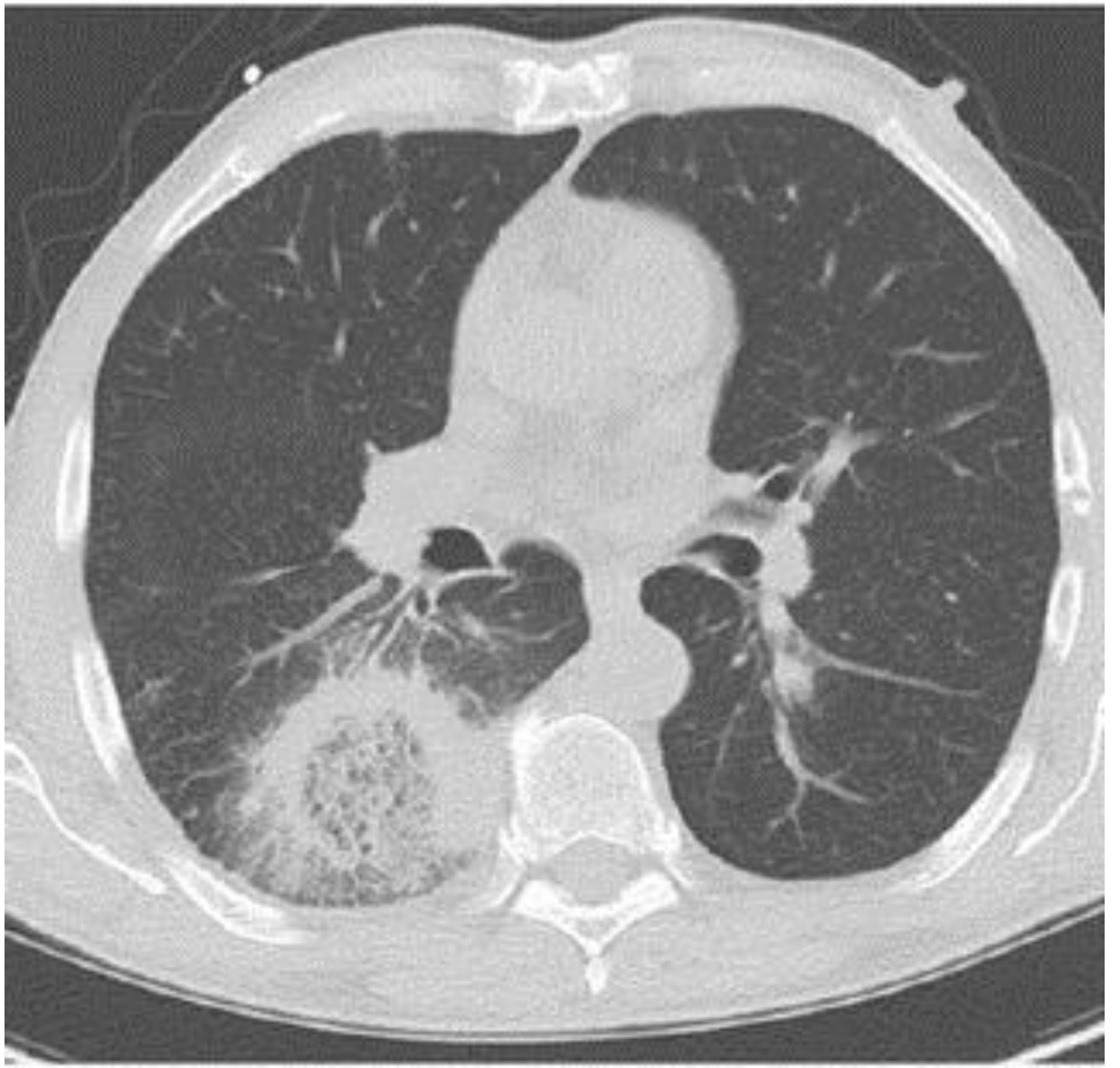
Slide courtesy of Kieren A. Marr, MD.

Caillot et al. *J Clin Oncol.* 2001:19:253-259.



*G. Desoubeaux et al. / Médecine et maladies infectieuses 44 (**2014**) 89–101*

Ters halo: Mukormikoz



İPA - Görüntüleme

Table 1. Imaging findings in patients with invasive pulmonary aspergillosis.

Imaging finding	No. (%) of patients (N = 235)
Macronodule (≥1 cm in diameter)[a]	222 (94.5)
Halo sign[b]	143 (60.9)
Consolidation[c]	71 (30.2)
Macronodule, infarct shaped	63 (26.8)
Cavitary lesion[d]	48 (20.4)
Air bronchograms	37 (15.7)
Clusters of small nodules (<1 cm in diameter)	25 (10.6)
Pleural effusion	25 (10.6)
Air crescent sign	24 (10.2)
Nonspecific ground-glass opacification	21 (8.9)
Consolidation, infarct shaped	18 (7.7)
Small-airway lesions[e]	16 (6.8)
Atelectasis	7 (3.0)
Hilar/mediastinal lesion	4 (1.7)
Pericardial effusion	2 (0.9)

NOTE. Patients may have >1 type of lesion.

[a] Includes macronodules with or without halo sign and infarct-shaped macronodules.

[b] A macronodule with a perimeter of ground-glass opacity.

[c] Includes infarct-shaped consolidations.

Reginald E. Greene et al. Clin Infect Dis. 2007;44:373-379

ESCMID: Görüntüleme ve BAL

Table 2
Recommendations for imaging and bronchoalveolar lavage

Population	Intention	Intervention[a]	SoR	QoE	Comment
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
	To identify vessel occlusion	Chest angio-CT/pulmonary CT angiography	B	II	
Haemoptysis	To identify vessel erosion	Chest angio-CT/pulmonary CT angiography	A	II	
Any, with infiltrate	To identify possible underlying fungal or other infectious disease	BAL	A	II	
Any, with infiltrate	To obtain appropriate specimens for microscopy, culture and PCR	CT-guided BAL	A	III	

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

[a] Diagnostic tests are interventions.

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

Immuno- PET / MRI

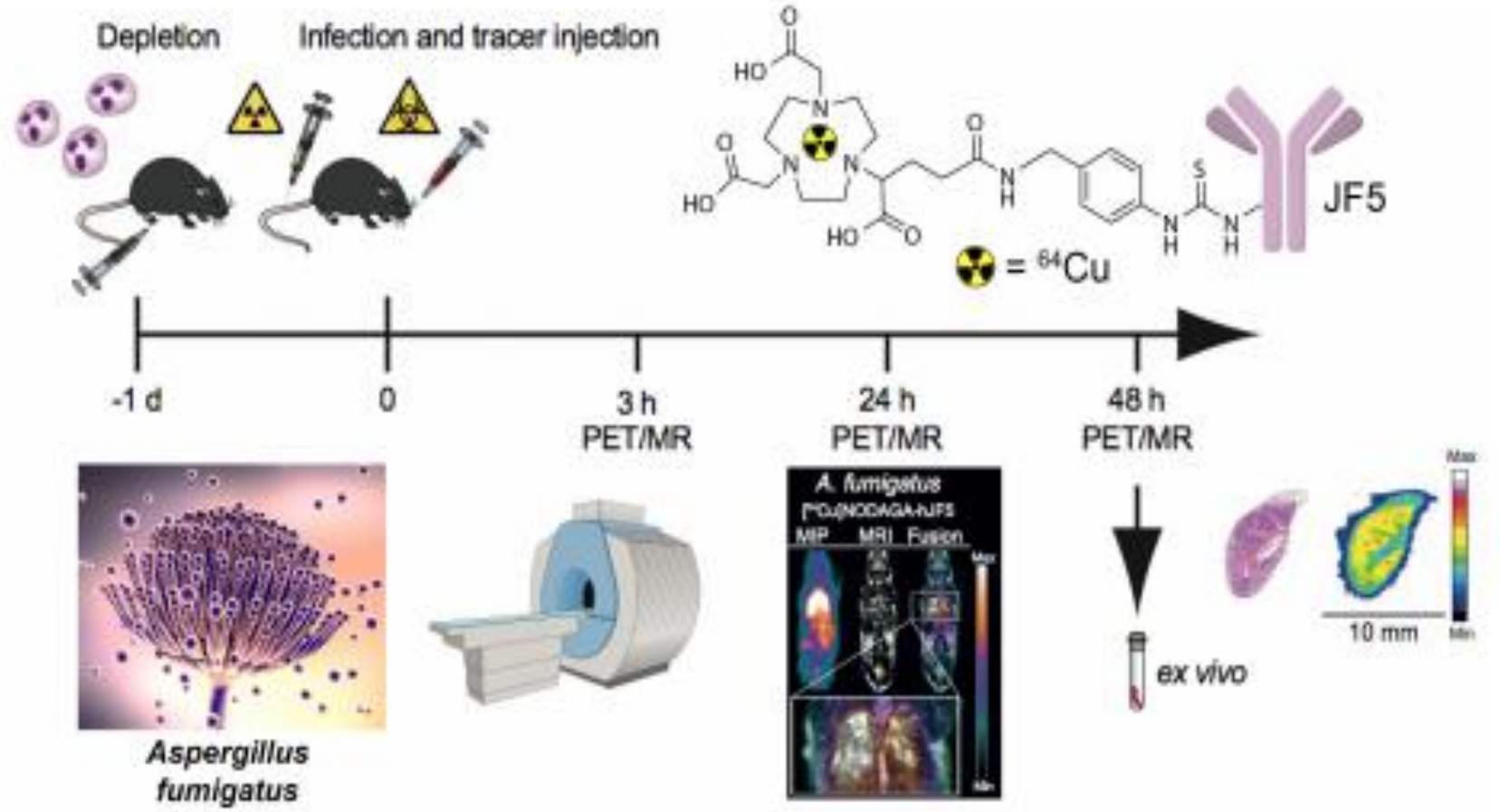


FIGURE 1 | Schematic representation of antibody-guided immunoPET/MR imaging of IPA in a neutropenic mouse model of disease. Twenty-four hours (−1 day) prior to infection with *A. fumigatus*, and administration of the PET tracer, neutropenia is induced in mice by the injection of 100 μg of the anti-Ly-6G/anti-Ly6C antibody RB6-8C5. At time 0, mice are infected by intratracheal injection with an *A. fumigatus* spore suspension and with simultaneous tail vein injection with a JF5-based PET tracer. The tracer shown is mAb JF5 conjugated to the positron emitter ^{64}Cu using the chelator NODAGA. Simultaneous PET/MR imaging of animals is then performed 3, 24, and 48 h after infection/tracer injection. *Ex vivo* bio-distribution and autoradiography are conducted after the last PET scan at 48 h. Adapted from Davies et al. (2017).

Immuno- PET / MRI

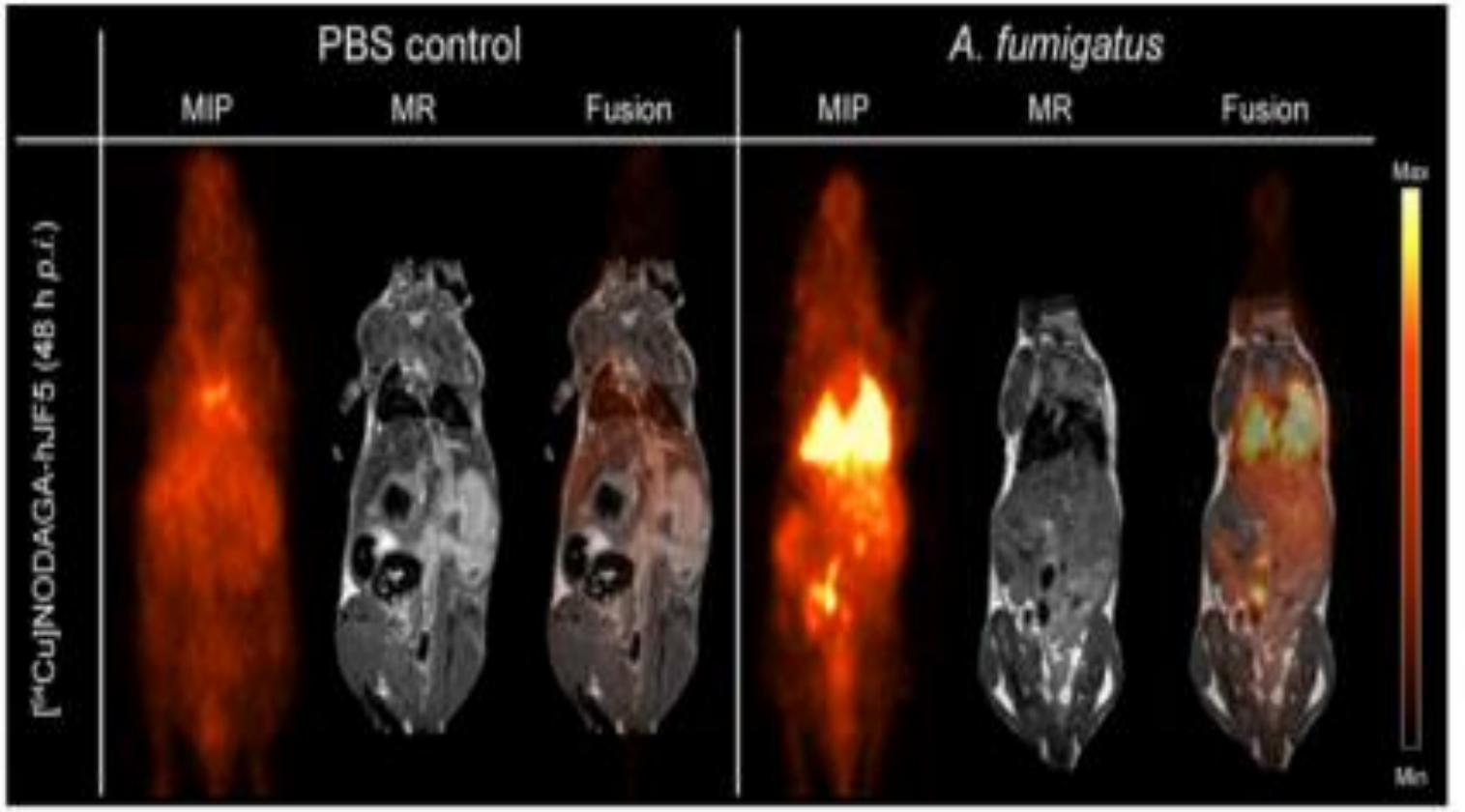


FIGURE 2 | ImmunoPET/MR imaging of IPA using the humanized *Aspergillus*-specific tracer [^{64}Cu]NODAGA-hJF5. The images show coronal maximum intensity projections (MIP), magnetic resonance (MR) imaging, and fused positron emission tomography (PET)/MR images of uninfected mice (PBS control) and mice infected with *A. fumigatus*. In order to render animals neutropenic, they received an intraperitoneal injection of the antibody RB6-8C5 and, 24 h later, were injected with the pathogen and [^{64}Cu]NODAGA-hJF5 tracer, according to the experimental procedure shown in **Figure 1**. Forty-eight hours after injection with the pathogen and humanized tracer, PET/MR imaging shows specific accumulation of the tracer in *A. fumigatus*-infected lung tissues. Image courtesy of MATHIAS Consortium.

TANI ve TEDAVİ ALGORİTMASI

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 A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

TANI ve TEDAVİ ALGORİTMASI

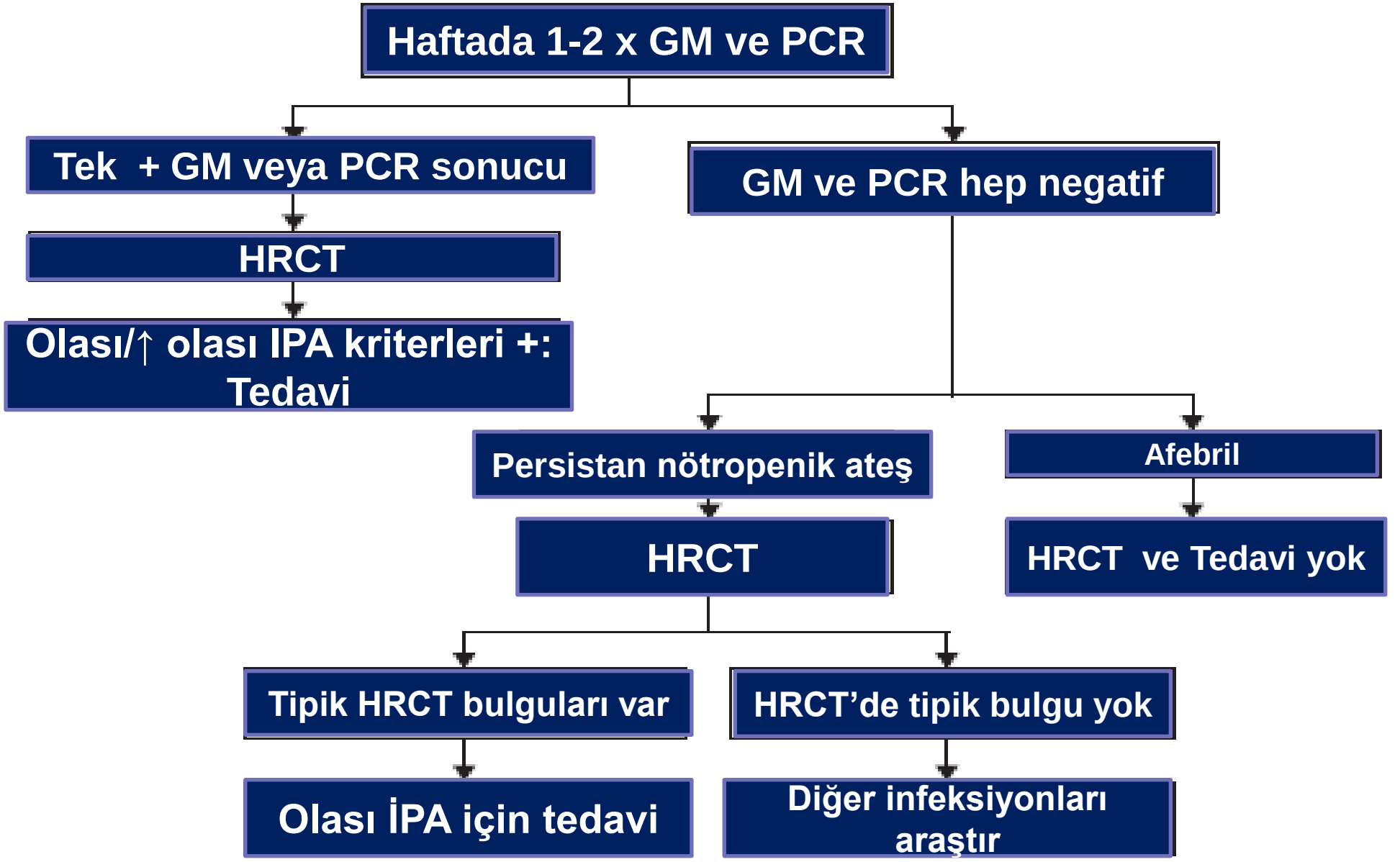
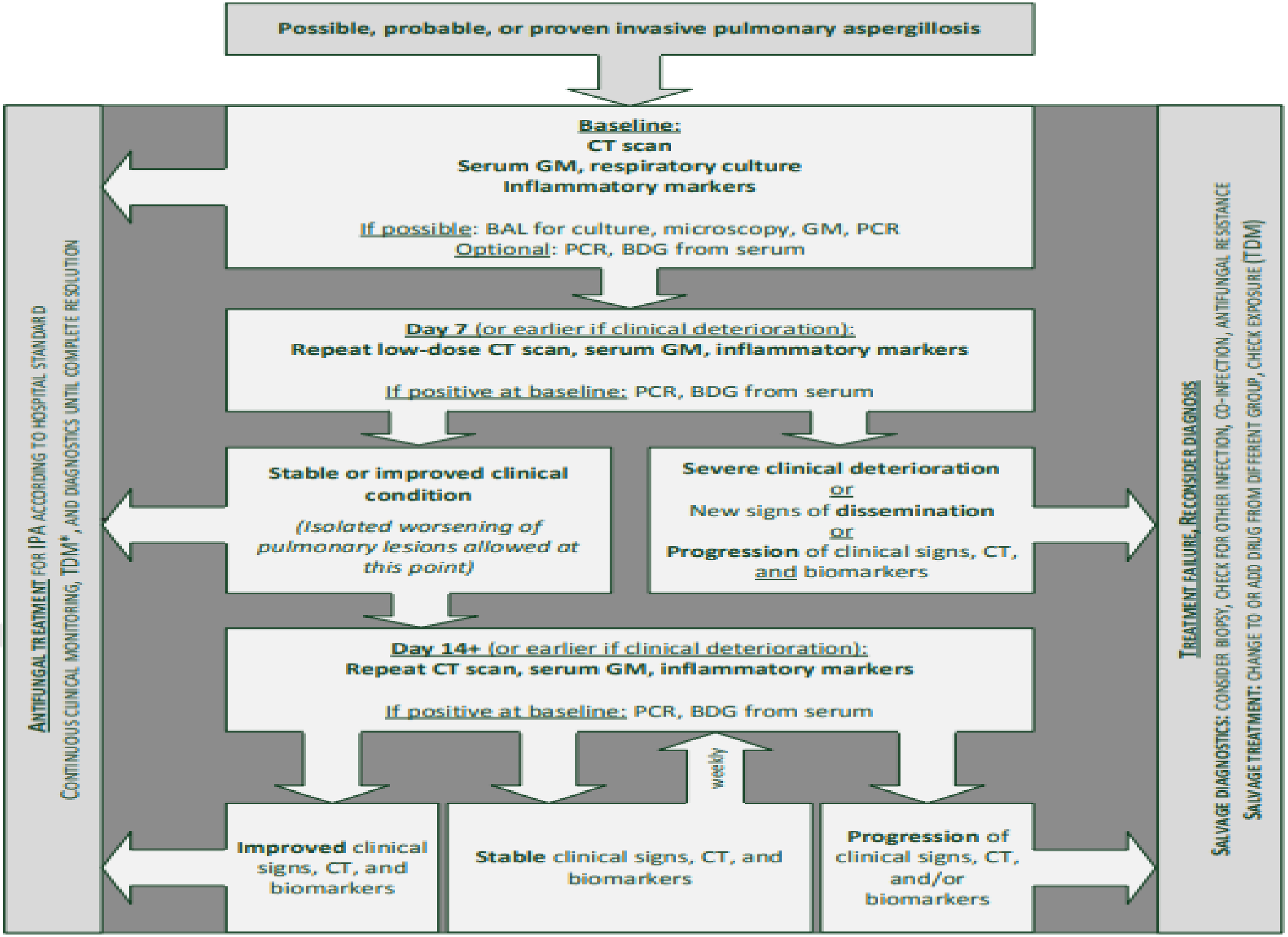


Figure 1: Diagnostic and treatment algorithm for the biomarker-based diagnostic strategy



TDM = Therapeutic Drug Monitoring, if applicable

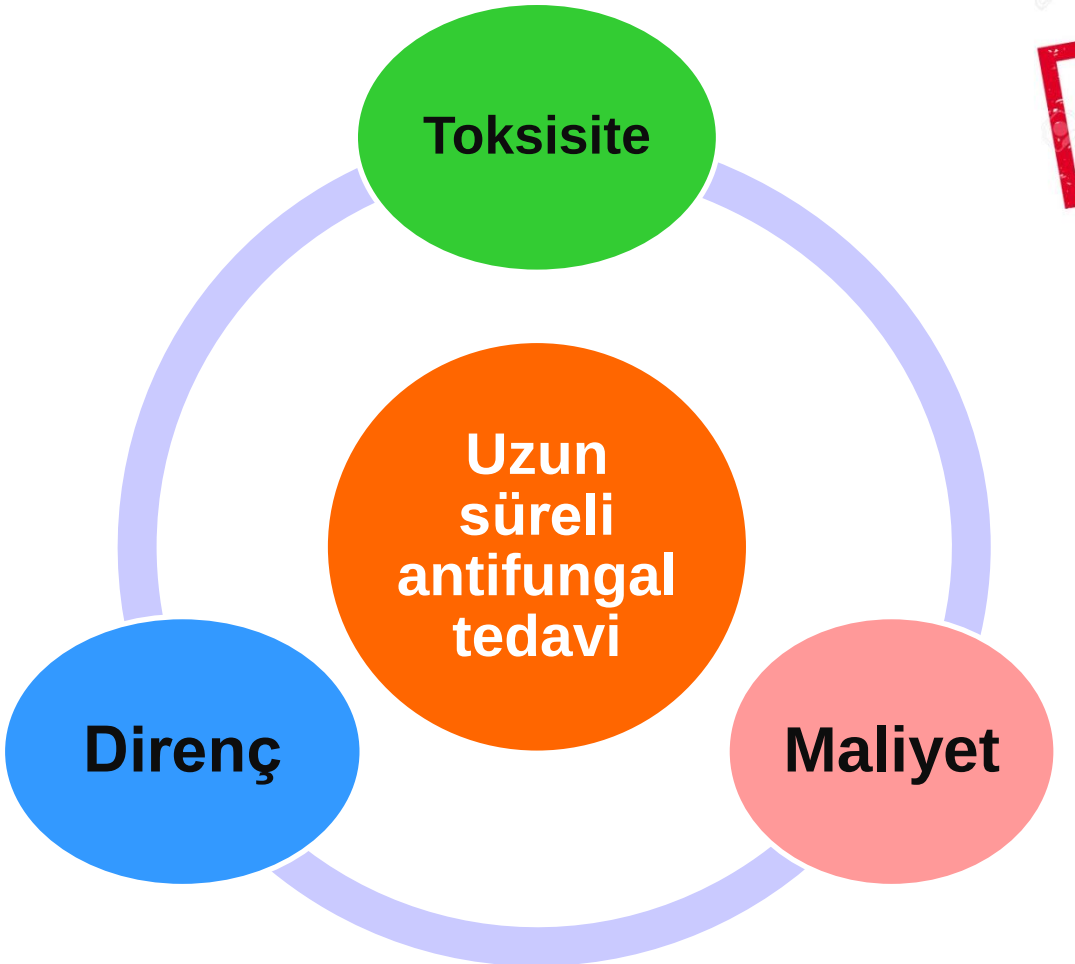
Heinz, W. J., Vehreschild, J. J., & Buchheidt, D. (**2018**).

TEDAVİ


RISK
ASSESSMENT


GUIDELINE


EARLY
DETECTION

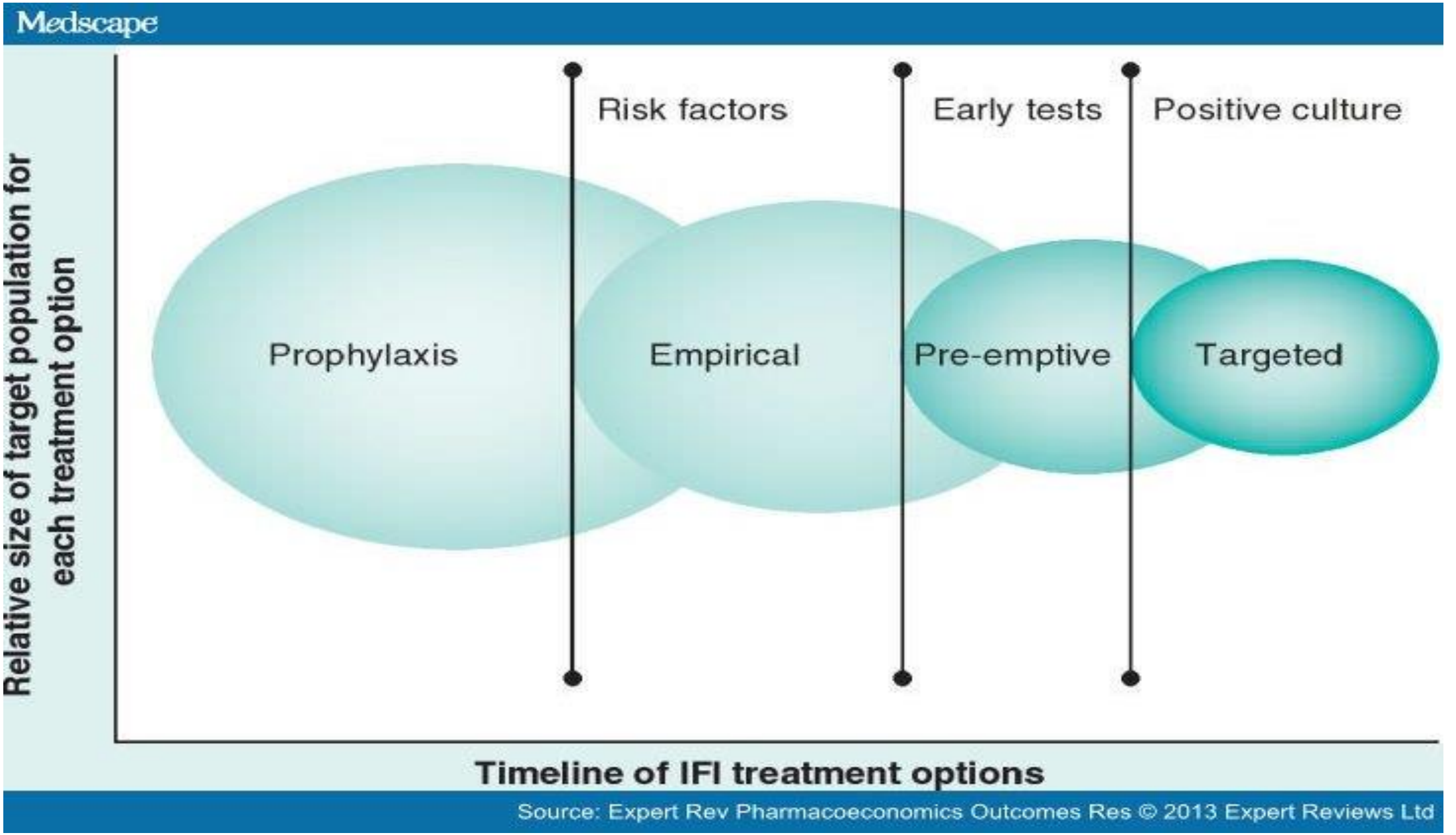

Toksisite
Uzun süreli antifungal tedavi
Direnç
Maliyet


Follow up!

TEDAVİ

- **Erken antifungal tedavi (Antifungal yönetim)**
  - Risk altındaki hastaların belirlenmesi ve izlenmesi
  - Antifungal tedavinin rehber önerileri doğrultusunda başlanması
  - Erken ve doğru tanı
  - Optimal antifungal ilaç seçimi
  - Antifungal tedavinin günlük gözden geçirilmesi ve de-eskalasyon
- **İmmunomodülasyon**
- **Cerrahi ?**

Muñoz P, et al. Antifungal stewardship in daily practice and health economic implications. Mycoses. **2015**;58(2):14-25


Medscape
Relative size of target population for each treatment option
Risk factors
Early tests
Positive culture
Prophylaxis
Empirical
Pre-emptive
Targeted
Timeline of IFI treatment options
Source: Expert Rev Pharmacoeconomics Outcomes Res © 2013 Expert Reviews Ltd

ANTİFUNGAL TEDAVİ

ERKEN ANTİFUNGAL TEDAVİ

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

- **Başlangıç Tedavisi**
- **Kurtarma Tedavisi**

- **Tedavi süresi:** Minimum 6-12 hafta
  - Tüm semptom ve bulgular düzelene kadar…

Empirik Tedavi

- Uzun süren nötropenili hastalarda

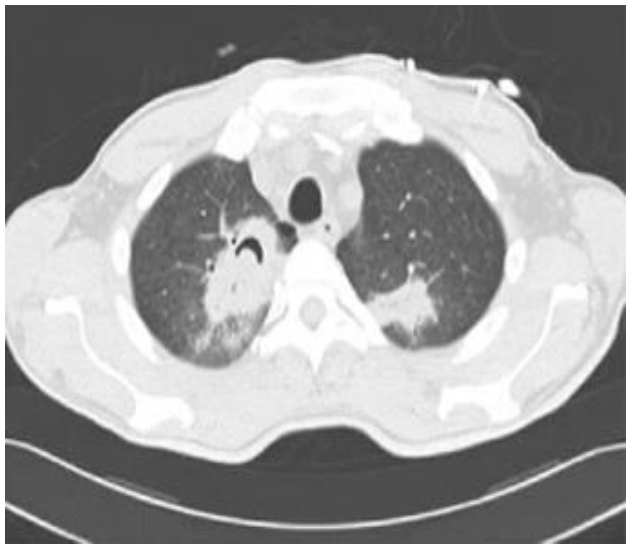
- **Persistan ateş + geniş spektrumlu antibakteriyel tedaviye yanıtsızlık**

- Tedavi sıklıkla **empirik** başlanmakta:
  - Klinik bulguları özgül değil
  - Kültür bazlı tanı yöntemlerinin sensitivitesi düşük
  - Üreme olduğunda kolonizasyon / infeksiyon ayrımı zor
  - Doku biyopsisi almak güç
  - Mortalite yüksek
  - **Tedaviyi erken başlama baskısı !**

Pre-emptif Tedavi

- **“Tanı-güdümlü” tedavi**

- Fungal infeksiyon lehine laboratuvar / görüntüleme bulgusu varsa;
  - **Galaktomannan ve/veya beta-D-glucan**
  - **Tipik HRCT bulguları**



BAŞLANGIÇ TEDAVİSİ

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

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

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

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 (mg/L)

- **İlaç etkileşimi** (kemoterapötikler !)

Vorikonazol

- **Yan etkiler:** görme bozukluğu
  halüsinasyonlar
  nöropati
  hafıza kaybı
  } geçici
  QTc interval uzaması
  alopesi
  cilt döküntüsü , periostit

- **IV** formülasyonları siklodekstrin aracı **"sulphobutylether-beta-cyclodextrin (SBECD)"** içerdiğinden **nefrotoksisite**

- Önceden renal hastalığı ve **CrCl <50 mL/min** olanlarda kullanılmamalı

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)

- **<u>Vorikonazol maruziyeti + mukormikoz ihtimali</u>** varsa…

- **Tedavi empirik başlanırsa, tanısal işlemlere devam edilmeli,**
  → IPA tanısı kesinleşirse, vorikonazole geçilmeli

- **Yan etkiler:** infüzyon ilişkili reaksiyonlar, elektrolit bozuklukları

İzavukonazol

- Ön-ilaç: **İzavukonazonyum 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.**

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) :

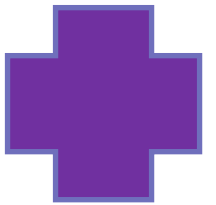
  1. gün: 200 mg IV yükleme, sonrasında 100 mg IV.

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

KURTARMA TEDAVİSİ

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

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



Caspofungin
veya
Mikafungin
veya
Anidulafungin

Antifungal duyarlık testleri

- *Aspergillus spp*'de **intrensek** polien veya azol direnci
- Azol maruziyeti sonrasında **kazanılmış** direnç

- Çevredeki azol fungisidlere maruziyet sonrası direnç, solunan havada dirençli sporlar

- Çevresel azol direnci <%10 ise primer seçenek değiştirilmemeli
- **>%10 direnç varsa; vorikonazol + ekinokandin / Amfo B**

- Tek bir örnekten üretilen farklı Aspergillus kolonileri farklı direnç profilleri barındırabilir → 5 koloniden duyarlılık çalışılmalı

Antifungal duyarlık testleri (anti-fungigram)

- Aspergillozda **rutin** olarak **önerilmez** (IDSA 2016)
  - Aspergillus türlerinde **tedavi yanıtı yoksa**,
  - **Azol direnci şüphesi**,
  - **Epidemiyolojik kanıt**
- *Aspergillus fumigatus* türlerinde triazol direnci hem önceden azol kullanmamış hem de kullanmış hastalarda belirlenmiş.
- *A. calidoustus*, *A. lentulus*, ve *Neosartorya udagawae:* birçok antifungale yüksek düzey intrensek direnç barındırır.

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

Vorikonazole yanıtsız IA

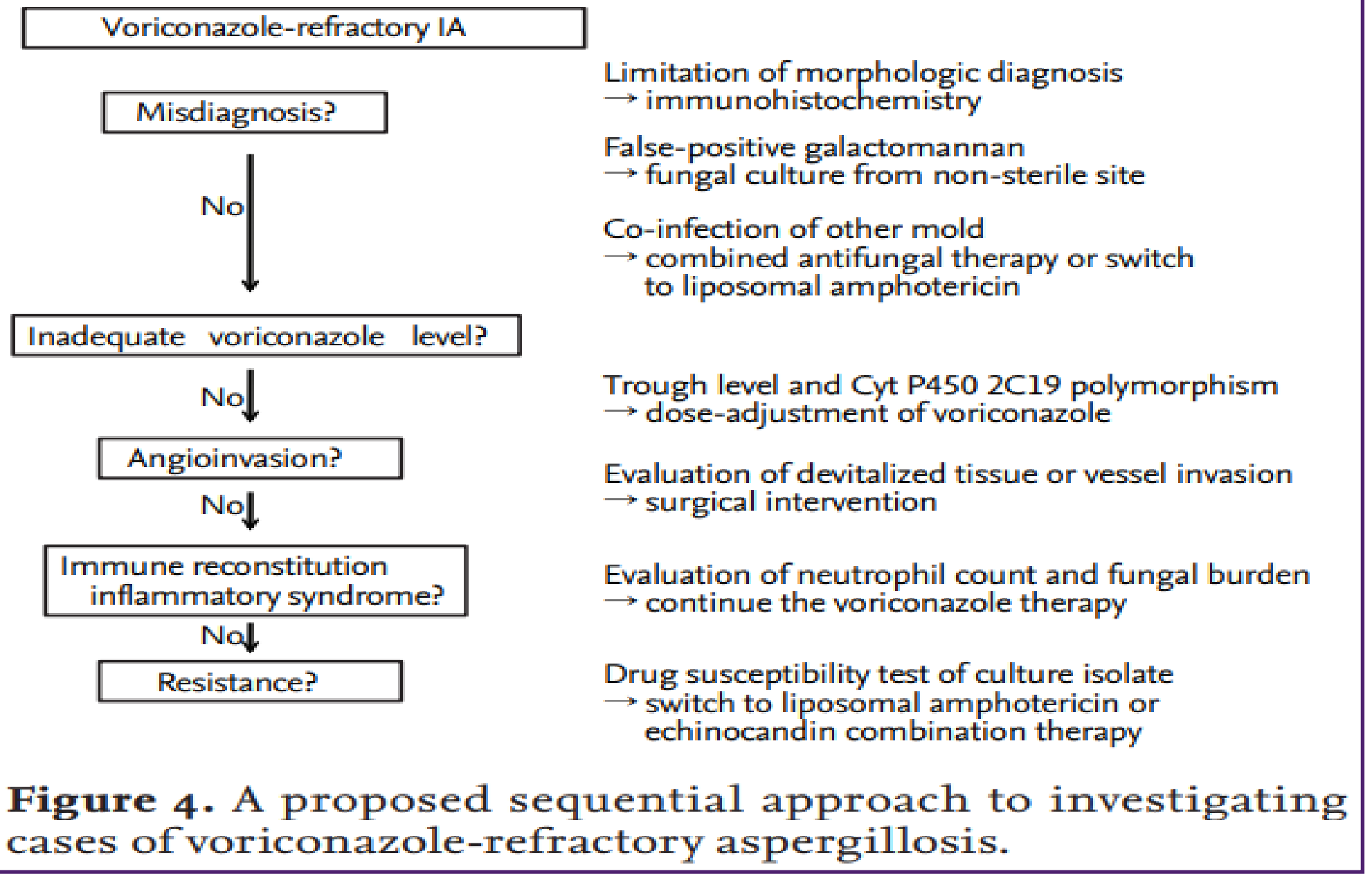


Figure 4. A proposed sequential approach to investigating cases of voriconazole-refractory aspergillosis.

Se Yoon Park, et al. Korean J Intern Med **2017**;32:805-812

İMMUNO-MODÜLASYON

- **İmmunosupresyonun azaltılması:**
  - Nötropenik hastalarda kemik iliği toparlanması İA kontrolü için kritik önemli
  - HSCT alıcılarında engrafman olmaması İA'a bağlı ölüme neden

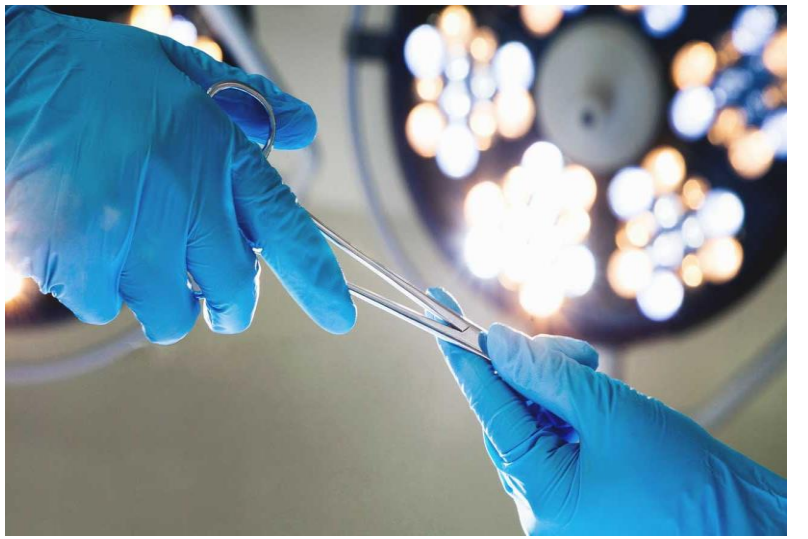
- **Koloni-stimulan faktörler (CSF):** Hasta bazında risk-yarar oranı
  - Nötrofil kemotaksisi ve fagositozu arttırır.
  - G-CSF nötropeni ve hospitalizasyon süresini kısaltır.
  - İnfeksiyona bağlı mortaliteyi azalttığına dair kesin kanıt yok

- **Granülosit Transfüzyonları:** Az sayıda hasta içeren çalışma verisi mevcut

İPA - CERRAHİ

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

- Genelde uygun değil
- **Komplikasyonlar:**
  - Kanama
  - İkincil enfeksiyonlar
  - İyileşmeyen yaralar



İNVAZİF PULMONER ASPERGİLLOZ REHBERLER

I. **2017 ESCMID-ECMM-ERS** guideline

II. **2016 IDSA** guideline

III. **2016 ECIL-6** guidelines

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

1. Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee38
2. Patterson TF, et al. Clin Infect Dis. 2016;63(4):e1.
3. Tissot. F, et al. Haematologica 2017, Vol102(3):433-444
4. Limper AH,et al. Am J Respir Crit Care Med. 2011;183(1):96.

IDSA 2016

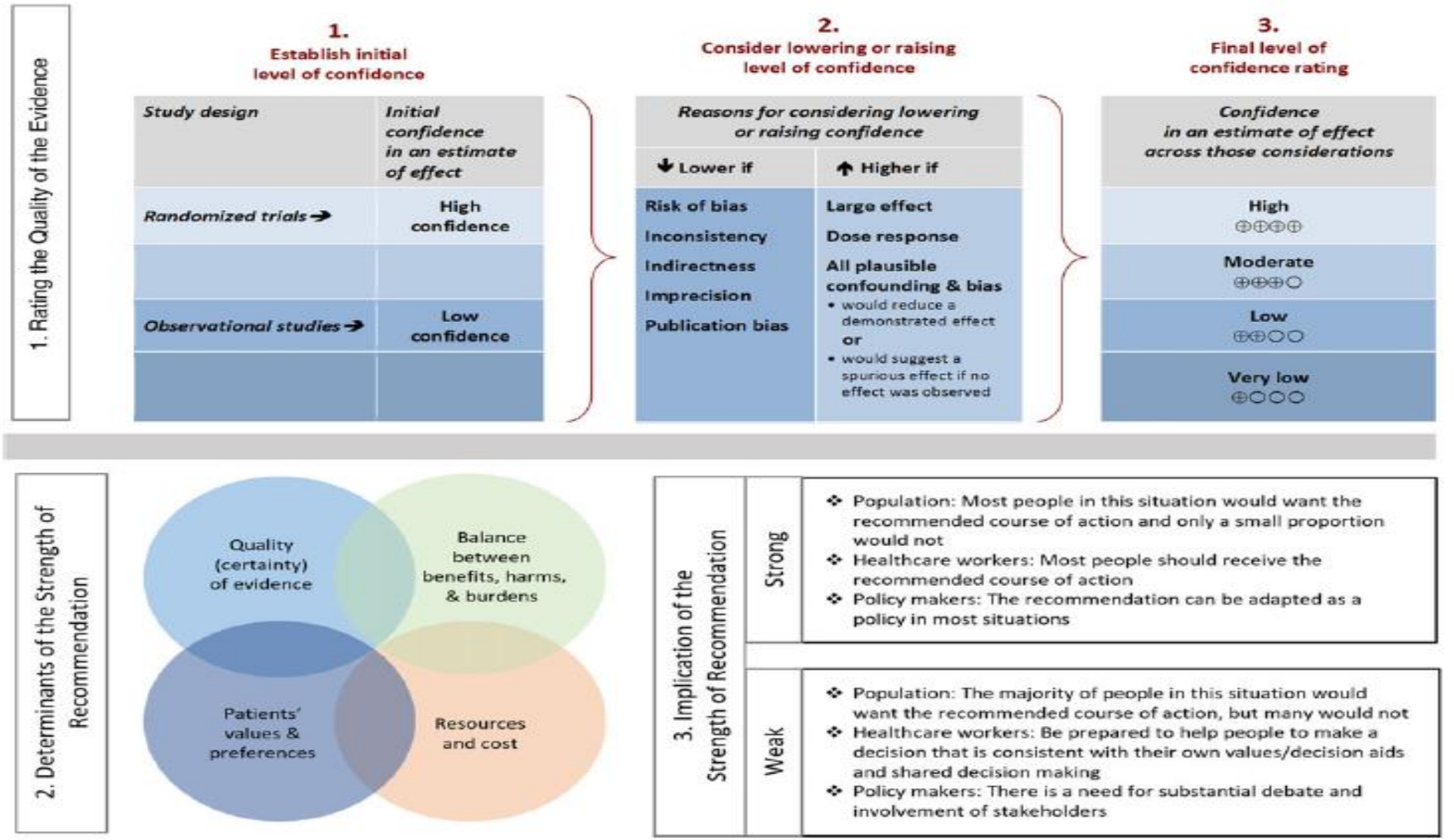


Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network) [4].

Clinical Infectious Diseases Clinical Infectious Diseases Advance Access published June 29, 2016

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

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

Thomas F. Patterson, et al. **2016 Update** by **IDSA**, CID June 29, 2016

IDSA 2016

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

	Primer Tedavi	Alternatif
IPA	Vorikonazol	**Primer:** Lipozomal AmB, İzavukonazol **Kurtarma:** ABLC, kaspofungin, mikafungin, posakonazol

Thomas F. Patterson, et al. **2016 Update** by **IDSA**, CID June 29, 2016

Tedavi sırasında ilaç-ilaç etkileşimi

İLAÇ /SINIF	ETKİLEŞİM
Kalsinörin inhibitörleri (KNI) ve mTOR* inhibitörleri	Azollerle KNI düzeylerinde belirgin artış
Kortikosteroidler	Azollerle düzeyleri artar
Antiretroviral İlaçlar	Değişken etkiler
Rifampin / Rifabutin	Rifampin / Rifabutin düzeyleri artarken azol düzeyleri azalır.
Vinkristin ve diğer vinka alkaloidleri	Azollerle birlikte nörotoksisiste (periferik nöropati ve nöbet), azol düzeyleri artar.
Siklofosfamid	Bazı azollerle düzeyi artar.
QT aralığını uzatan ilaçlar (FQ, makrolid, antiaritmikler, Ca kanal blokerleri, antihistaminikler , psikiyatrik ilaçlar etc)	QT aralığı uzar, azollerle kardiyak aritmi gözlenebilir.

mTOR*: mammalian target of rapamycin

Thomas F. Patterson, et al. **2016 Update** by **IDSA**, CID June 29, 2016

Tedavi sırasında terapötik ilaç monitorizasyonu

KLİNİK SENARYOLAR	ÖRNEKLER, YORUM
Farmakokinetik değişkenlik	IV'den po'e geçiş, hepatik, renal, GI fonksiyon değişikliği, fizyolojik instabilite
Etkileşen ilaçlar	CYP3A4, anti-asit, PPI (itrakonazol kap, posakonazol süsp), ART, steroidler (vorikonazol)
Ağır hastalık	Yaygın, kritik yapılara yakın, multi-fokal Hastalık, SSS infeksiyonu
Tedavi uyumu	Uzun süreli konsolidasyon tedavisi veya sekonder profilakside önemli
Olası "breakthrough" / geri tepme infeksiyonu	Yetersiz antifungal maruziyetinde fungal hastalık progresyonu ?
Olası ilaç toksisitesi Vorikonazol: nörotoksisite	Hepatotoksisite için net tanımlanmış

Thomas F. Patterson, et al. **2016 Update** by **IDSA**, CID June 29, 2016

European Conference on Infections in Leukemia (ECIL)

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 : 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(3)

ECIL-6 : İA Kurtarma Tedavisi

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.

Tissot F, et al.Haematologica | 2017; 102(3)

Refrakter ya da Progresif Aspergilloz – Kurtarma Tedavisi

- **Radyolojik olarak progresyon kanıtı, devam eden GM pozitifliği**

- Mevcut tedaviye bir antifungal ajan eklenebilir
- Ya da başlangıç rejimi dışındaki sınıflardan antifungal ajan kombinasyonu yapılabilir (zayıf öneri, orta kanıt düzeyi)

- Kurtarma tedavisinde kullanılabilecek ajanlar:

  LAmB, mikafungin, kaspofungin, **posakonazol** veya **itrakonazol** (güçlü öneri; orta kanıt düzeyi)

- Başlangıçtaki triazol tedavisine yanıtsızlık varsa LAmB ± ekinokandin düşünülmelidir

IDSA 2016, ESCMID 2017

ARTICLE IN PRESS

Clinical Microbiology and Infection xxx (2018) e1–e38

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Original article

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],

- ***A. fumigatus* vorikonazol MIC =2 mg/L** (IM) ile infekte hastaların vorikonazol monoterapisine daha az yanıt verip vermedikleri net değil. Bu hastalarda tedavi yetersizliği olasılığı yüksek olduğundan invaziv aspergilloz durumunda **ekinokandin ya da LAmB ile kombine tedavi** düşünülmeli (AIII)
- Çevre izolatlarında azol direnci <%10 ise yaklaşım primer tedavi şeklinde
- **Azol direnci >%10** ise primer tedavide **vorikonazol + ekinokandin** (BIII) veya **vorikonazol + LAmB** (BIII)

Ullmann A.J., et al. ESCMID -Clinical Microbiology and Infection (2018), e1ee382.

ESCMID: Birinci basamak hedefe yönelik tedavi

Table 27
Targeted therapy of pulmonary disease—first line

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment
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
		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
		L-AmB 3 mg/kg	B	II	II_t	II_t	
		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
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	C	II	II	II	
		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
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III	
		Micafungin 100 mg	C	III	III	III	
		AmB colloidal dispersion (ABCD) 4–6 mg/kg	D	I	II_t	II_t	
		Conventional AmB 1–1.5 mg/kg	D	I	II_t	II_t	
		Other combinations	D	III	III	III	Efficacy unproven
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III	

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

ESCMID: Azol direnci varlığında optimal tedavi

Table 20

Optimal therapy in documented azole-resistance

Population	Intention	Intervention	SoR	QoE	Comment
Isolate with voriconazole MIC = 2 mg/mL	To cure IA	Voriconazole + echinocandin combination therapy or L-AmB monotherapy for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2
Isolate with voriconazole MIC >2 mg/mL	To cure IA	L-AmB	A	II_u	
		AmB lipid complex	C	III	
		Voriconazole & anidulafungin	B	III	
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB and other azoles

Abbreviations: AmB, Amphotericin B; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; L-AmB, liposomal amphotericin B; QoE, Qu
Strength of recommendation.

Ullmann A.J., et al. Clinical Microbiology and Infection (2018), e1ee382.

Aspergilloz AFY programı - Demet önerileri

- Tanı için galaktomannan testi, ince kesitli /yüksek rezolusyonlu BT ve mümkünse solunum yolu örneklerini almak,
- Tedavi için mevcut rehberlerin ilk seçenek önerilerini kullanmak,
- Kombinasyon tedaviyi sadece kurtarma tedavisine kısıtlamak,
- Tedavi başlangıcından 2 hafta içerisinde vorikonazol serum düzeyi izlemek.

Muñoz P, et al. Antifungal stewardship in daily practice and health economic implications. Mycoses . 2015 ;58 Suppl 2:14-25

Geliştirilmekte olan YENİ ANİFUNGAL 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

Expert Review of Respiratory Medicine

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Special Considerations for the Diagnosis and Treatment of Invasive Pulmonary Aspergillosis

Matthew William McCarthy & Thomas J Walsh

- The use of nucleic acid amplification assays such as **real-time, quantitative PCR (qPCR)** to diagnose IPA remains an area of active inquiry but is not yet available at most medical centers.
- **Resistance to triazoles in *A. fumigatus*** has been reported **in azole-naive patients** in Europe, Asia, Australia and North America and in 2017. Azole-resistant *A. fumigatus* was reported from samples taken from flower fields in Colombia.
- There is an increasing interest in the potential of **exhaled biomarkers**, such as **volatile organic compounds (VOCs),** to improve accurate diagnoses and management decisions in patients with suspected IPA
- The **oral glucan synthase inhibitor SCY-078** has activity against *Aspergillus spp.* and its role in the treatment of invasive fungal infections is being investigated.

Matthew William McCarthy & Thomas J Walsh (2017)

MARUZİYETTEN 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).

Ullmann A.J., et al. ESCMID -Clinical Microbiology and Infection (2018), e1ee382.

KORUNMA - Primer Profilaksi

- **Yüksek riskli hastalar:**
  - Uzamış-derin nötropeni,
  - Allo- HSCT aktif GVHD,
  - İndüksiyon KT alan AML/ MDS hastaları
- **İlaç yan etkileri**
- **İlaç etkileşimleri**
- **Maliyet**
- **Potansiyel direnç gelişimi**

- **Küflere etkili ajanlar**
  - Primer:
    - **Posakonazol*****
  - Alternatif:
    - Vorikonazol
    - İtrakonazol

KORUNMA - Sekonder Profilaksi

- **İA için tedavi alanlarda reaktivasyon riski**
  - Latent subklinik infeksiyonun reaktivasyonu
    - Anjiyo-invazyon, ilaç penetrasyon güçlüğü, hematolojik kanserin remisyonda olmaması, nötropeni süresi, sistemik kortikosteroid vb.
  - Kemoterapi veya HSCT sonrası
  - Vorikonazol veya küflere etkili başka bir antifungal ilaç
  - Önceki etken ve yanıta göre seçim

KORUNMA

- Antifungal profilakside spektrum, yan etkiler, uyum, maliyet, eşlik eden durumlar, kullanım yolu önemlidir.
- Hangi ajanın profilakside seçileceği konusunda rehberler yol göstericidir.
- **Yüksek riskli hastada**; KİT, GVHD, AML indüksiyon gibi durumda **profilakside posakonazol** önerilmiştir.
- Bunun dışındaki durumlarda flukonazol profilaksisi maliyet açısından uygun, etkilidir.

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