KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Bilimle Sağlıkla 37.YIL

İnvazif Fungal İnfeksiyonlar:
Tanı ve Tedavisi

# İnvazif Aspergilloz

# Tanı ve Tedavisinde Güncel Gelişmeler

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Koç Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

30.05.2023

# Sunum Planı

## İnvazif Aspergilloz

- Değişen epidemiyoloji
  - ✓ Farklı riskli gruplar
- İA Tanısında güncellemeler
- İA Değişen Direnç durumu
- Antifungal Yönetim
- Soru & Katkı

# 2020 First WHO Fungal Priority Pathogen List


- ✓ *Candida auris*
- ✓ Azole-resistant *Candida spp*.
- ✓ **Azole-resistant *Aspergillus fumigatus***
- ✓ *Cryptococcus neoformans* (& *C. gattii*)
- ✓ *Pneumocystis jirovecii*
- ✓ *Mucorales*
- ✓ Potentially Histoplasmosis

Global **public health importance** based on **limitations of treatment** options due to **resistance** and/or **treatability issues**

WHO Antifungal Expert Group Priority Fungal Pathogens. Report. Geneva: WHO; 2020.

World Health Organization (WHO) Fungal Priority Pathogens List, 2022 [6].

| Critical priority | High priority | Medium priority |
|---|---|---|
| *Aspergillus fumigatus* | *Candida glabrata* | *Candida krusei* |
| *Candida al* | | *s spp.* |
| *Candida au* | | *us gattii* |
| *Cryptococc neoforman* | | *ora* |
| | | *oides spp.* |
| | | *tis jirovecii* |
| | *Mucorales/Mucormycosis* | *Scedosporium spp.* |
| | | *Talaromyces marneffei* |

The **COVID-19 pandemic**, **climate change** and changes in **human** and **animal habitation**, **increased resistance to antifungal drugs**, and an increased number of **immunocompromised patients** have driven a recent global surge in pathogenic fungal infections.

Adapted from: WHO fungal priority pathogens list to guide research, development and public health action. 25 October 2022 [6].

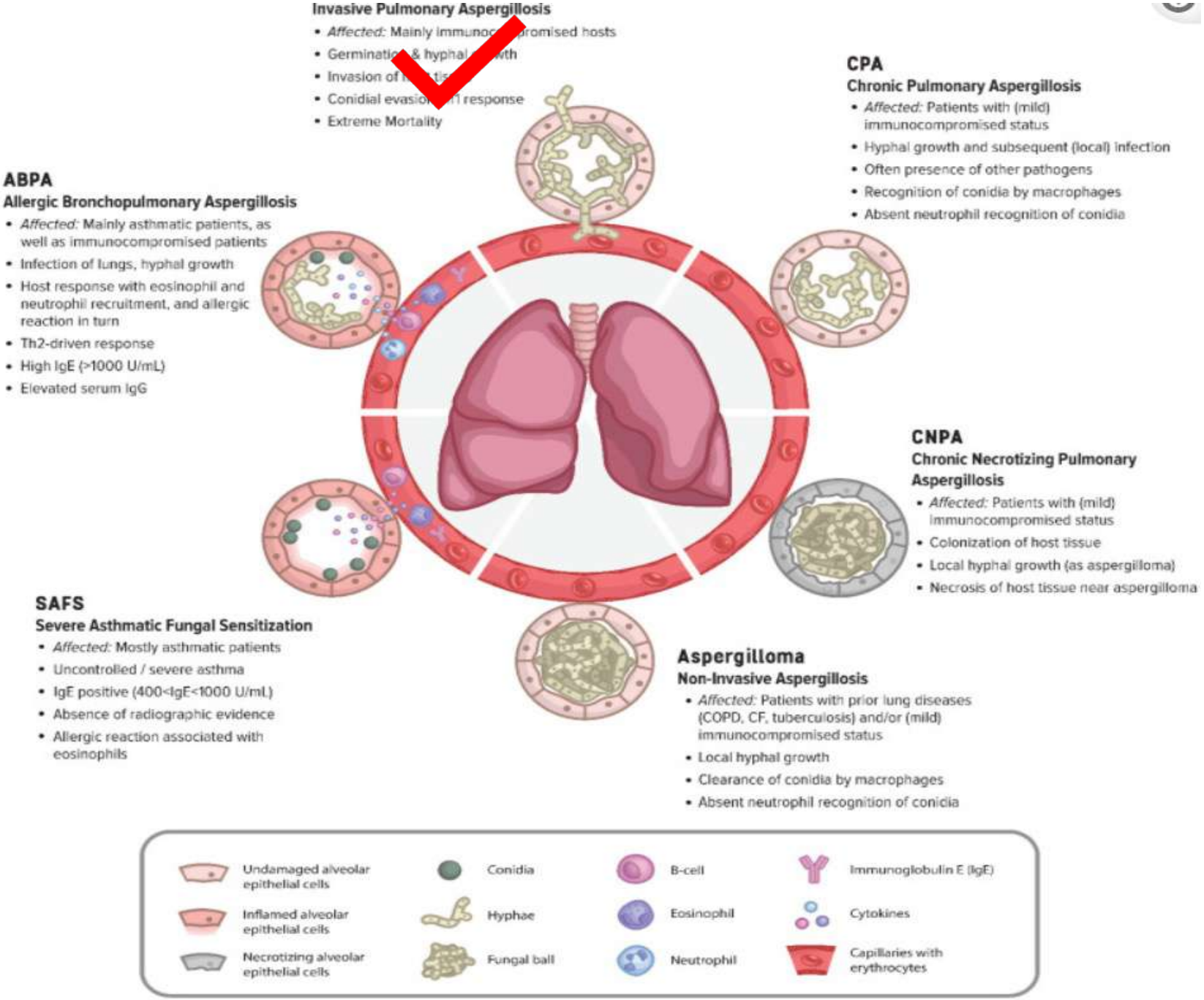
*Fungal causes of eumycetoma include *Madurella mycteomatis*, *Aspergillus spp.*, *Nocardia spp.*, *Fusarium spp.*

World Health Organization (**WHO) Report**. *WHO fungal priority pathogens list to guide research, development and public health action.* **Oct 25, 2022**.

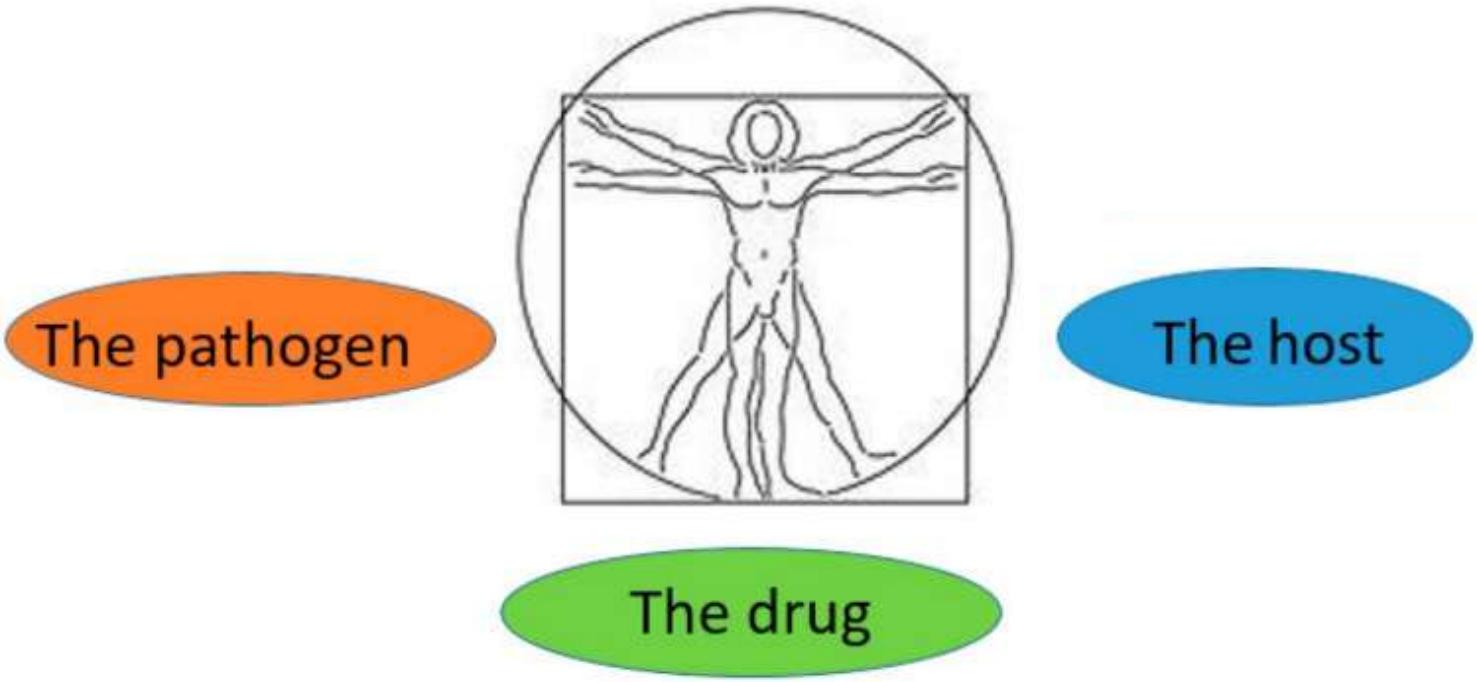
**Soru(n) 1**

İnvazif Aspergilloz **epidemiyolojisinde**

değişiklik var mı?




*J Fungi* (Basel). 2022;8(8):758.



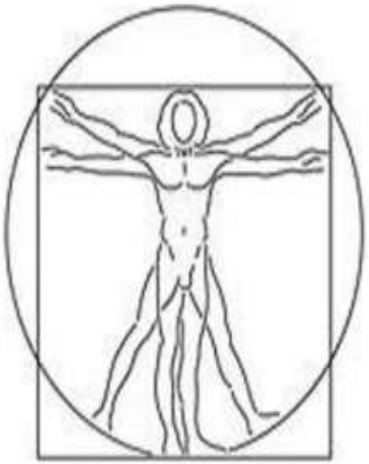

*Ther Drug Monit*. 2022;44:66–197

***Aspergillus***
***Mucorales***
***Candida***
***Histoplasma***
***Cryptococcus***
***Trichosporon***

**Localization**
CNS
Disseminated
Pulmonary

**Susceptibility**
MIC
Resistance

The pathogen



**Underlying disease**
Immunocompromised
Oncohematology
HSCT
SOT
Immunocompetent
Burn wound injury
Diabetes

**Pre-existing factors**
Age
CYP
Ethnicity
Obesity
Cystic fibrosis

**Co-existing factors**
Renal function
Liver function
Inflammation
ICU
ECMO
CV19

The host

The drug

**Treatment**
Prophylaxis

Breakthrough infection
Curative, salvage
Maintenance

TDM recommendation

***AmB***
***Echinocandins***
***5FC***
***Azoles*** ***FCZ***
***ISZ***
***PSZ***
***ITZ***
***VRZ***

**TDM rationale**
Safety/toxicity
Liver
Kidney
Neuro
PK variability
DDI

**TDM issues**
Sampling, time of sampling
Analytics
Routes of administration
IV
Oral, tablet
Nasogastric
PK/PD parameters
Software
PKPB modeling

*after Lindholm 1995*

*Ther Drug Monit*. 2022;44:66–197

Review > J Fungi (Basel). 2021 Oct 10;7(10):848. doi: 10.3390/jof7100848.

# Changing Epidemiology of Invasive Fungal Disease in Allogeneic Hematopoietic Stem Cell Transplantation

Pedro Puerta-Alcalde [1], Carolina Garcia-Vidal [1]

**Allogeneik Hematopoetik Kök Hücre Naklinde**

İnvazif Mantar İnfeksiyonunda Değişen Epidemiyoloji

- Yıllar için **kandidemi** oranları **azalmakta**
- En çok izole edilen mantar ***Aspergillus fumigatus***
  - *Aspergillus niger*
  - *Aspergillus terreus*
  - *Aspergillus flavus*

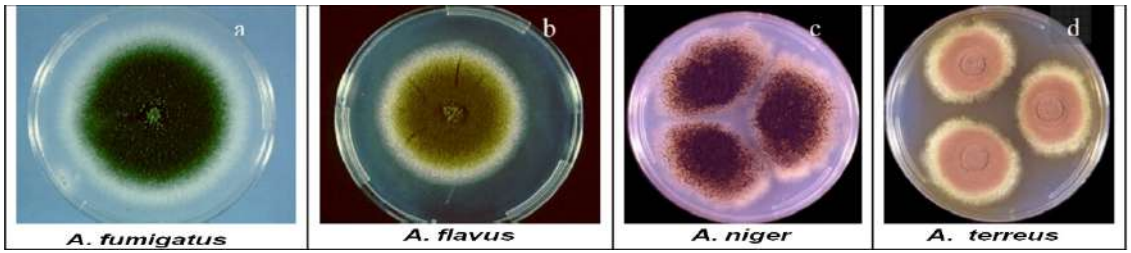


Table 1. Important studies regarding invasive fungal disease in allogenic HSCT recipients.

| Reference and Year of Publication & | Study Type and Period | n | Prophylaxis | IFD Incidence | IFD Epidemiology |
|---|---|---|---|---|---|
| Martino et al. [11] 2002 | Retrospective study 1996–2000 | 395 allo-HSCT | 73% fluconazole, 17% itraconazole, 4% amphotericin B, 6% no prophylaxis | 14% | 64% aspergillosis, 20% candidiasis, 6% mucormycosis, 6% other |
| Pagano et al. [12] 2007 | Retrospective study 1999–2003 | 1249 allo-HSCT | 39% fluconazole, 21% itraconazole | 8% | 81% aspergillosis, 14% candidiasis (50% non-*albicans*), 3% fusariosis, 2% other molds |
| Garcia-Vidal et al. [21] 2008 | Retrospective study 1998–2002 | 1248 allo-HSCT | Not reported | 13% invasive mold disease | 87% aspergillosis, 4% fusariosis, 3% mucormycosis |
| Neofytos et al. [20] 2009 | Prospective study 2004–2007 | 161 IFD in allo-HSCT | Not reported | Not applicable | 57% aspergillosis, 25% candidiasis, 7% mucormycosis, 8% other molds |
| Kontoyiannis et al. [19] 2010 | Prospective study 2001–2005 | 6666 allo-HSCT | Not reported | ≈8% | 43% aspergillosis, 28% candidiasis, 8% mucormycosis, 10% other molds |
| Nucci et al. [22] 2013 | Prospective study 2007–2009 | 378 allo-HSCT | 81% fluconazole, 1% itraconazole, 4% voriconazole, 4% amphotericin B | 11% | 35% fusariosis, 30% aspergillosis, 17% invasive candidiasis, and 12% hyalohyphomicosis |
| Girmenia et al. [23] 2014 | Prospective study 2008–2010 | 1858 allo-HSCT | 75% fluconazole, 14% mold-active prophylaxis (NS), 5% secondary prophylaxis (NS), 6% no prophylaxis | 9% | 81% aspergillosis, 11% candidiasis, 4% mucormycosis, 2% fusariosis, 1% other molds, 1% rare yeasts |
| Sun et al. [24] 2015 | Prospective study 2011 | 1053 allo-HSCT | 61% fluconazole, 22% itraconazole, 19% voriconazole | 9% | 33% aspergillosis, 13% candidiasis, 54% non-identified |
| Gomez et al. [25] 2018 | Retrospective study Pediatric patients 1998–2016 | 143 allo-HSCT | Fluconazole or voriconazole (rates not reported) | 13% | 86% candidiasis, 17% aspergillosis |
| Linke et al. [26] 2019 | Retrospective study Pediatric patients 2005–2015 | 221 allo-HSCT | 52% fluconazole, 9% mold-active azole, 32% liposomal amphotericin B, 1% micafungin, 6% no prophylaxis | 7% | 73% aspergillosis, 27% candidiasis |
| Souza et al. [27] 2020 | Prospective study 2015–2016 | 71 allo-HSCT | 68% fluconazole, 17% micafungin, 11% mold-active azole (NS) | 11% | 50% aspergillosis, 38% candidiasis, 12% other molds |

J Fungi (Basel). 2021 Oct 10;7(10):848.

# Invasive aspergillosis in solid organ transplant patients: diagnosis, prophylaxis, treatment, and assessment of response

Dionysios Neofytos[1*], Carolina Garcia-Vidal[2], Frédéric Lamoth[3,4], Christoph Lichtenstern[5], Alessandro Perrella[6,7] and Jörg Janne Vehreschild[8,9,10]

| Population | Incidence (%) | Overall mortality (%) | References |
|---|---|---|---|
| Heart | 3.5–26.7 | 36–66.7 | [1, 3, 5, 8, 9] |
| Kidney | 1.2–4 | 4–25 | [1, 3, 5] |
| Liver | 1–4.7 | 83–88 | [1, 3, 5] |
| Lung | 8.3–23.3 | 4.2 | [1, 3, 5] |

- **SOT** alıcılarında **IA tanısı** yüksek derecede **farkındalık** gerektirir
- Standard **tanı** yöntemleri, nötropenik hastalarda gözlemlenen **duyarlılığı** ve **özgüllüğü sağlamayabilir**.

Neofytos et al. *BMC Infectious Diseases.* **2021**; 21:296

Multicenter Study > Clin Infect Dis. 2021 Oct 5;73(7):e1634-e1644. doi: 10.1093/cid/ciaa1298.

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

P Lewis White [1], Rishi Dhillon [1], Alan Cordey [1], Harriet Hughes [1], Federica Faggian [1],

**YBÜ'de İFİ**

- **İnsidansı %26.7**; **%14.1 aspergillo**z, **%12.6 maya** infeksiyonları
- Toplam **mortalite** hızı **%38**; İFİ **olanlarda %53,** olmayanlarda **%31** (P: 0.03).

**Mortalite:**

- ✓ **Antifungal** alanlarda **%38.5** & almayanlarda **%90** (P: 0.008)
- ✓ **Kortikosteroid** kullanımı (P: 0.007)
- ✓ **Kronik AC hastalığı** varlığı aspergillozda **mortaliteyi** ciddi **artırmakta** (P: 0.05)

International Journal of Environmental Research and Public Health

*Int J Environ Res Public Health*. **2022**; 19: 7079.

MDPI

*Article*

# Tendency in Pulmonary Aspergillosis Investigation during the COVID-19 Era: What Is Changing?

Giuseppina Caggiano [1,*], Francesca Apollonio [1], Mila Consiglio [2], Valentina Gasparre [2], Paolo Trerotoli [1], Giusy Diella [1], Marco Lopuzzo [2], Francesco Triggiano [2], Stefania Stolfa [1], Adriana Mosca [1] and Maria Teresa Montagna [1]

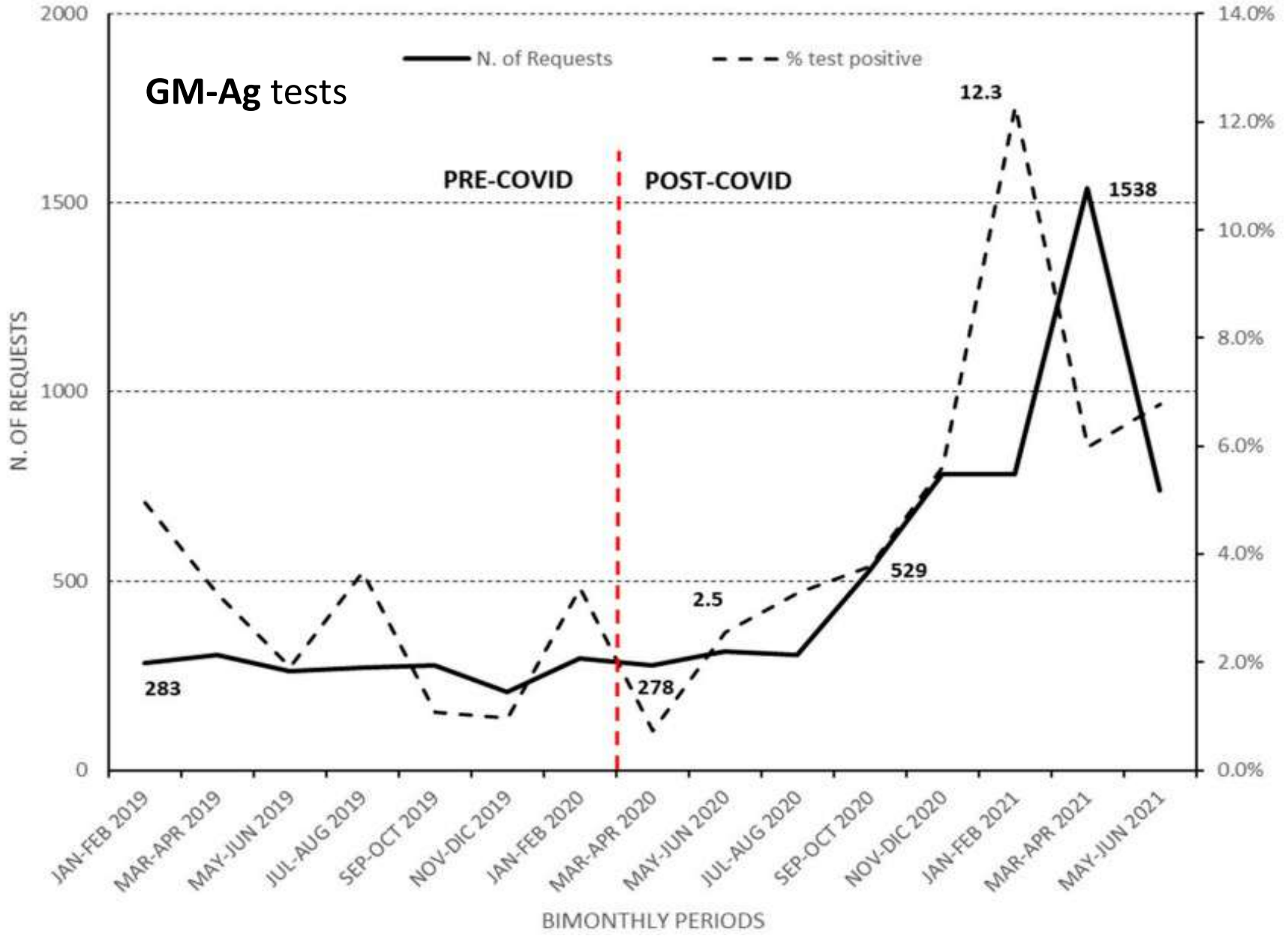
**COVID-19** hastalarında ***Aspergillus* spp. ko**-infeksiyonlarını (**CAPA**)

**Tanı güç**: CAPA klinik olarak karmaşık ve bronkoskopi yapmak zor.

**İPA** tanısı **mikrobiyolojik** yöntemler ve BAL veya serumda **Galaktomanan** (sGM)

**Çalışmanın amacı**, COVID-19 döneminde **İPA**'da artışı tespit etmek.

Güney **İtalya**'da Ocak 2019- Şubat 2020 ile Mart 2020- Haziran 2021 arasında **1550** yataklı hastanede 32 farklı klinikte yapılmış




*Int J Environ Res Public Health*. 2022; 19: 7079.

| Departments | Pre-COVID Period | | COVID Period | | Total | |
|---|---|---|---|---|---|---|
| | No. of Positive Tests/No. of Total Tests | Positive Tests (%) | No. of Positive Tests/No. of Total Tests | Positive Tests (%) | No. of Positive Tests/No. of Total Tests | Positive Tests (%) |
| Oncohematology | 22/1428 | 1.5 | 48/1330 | 3.6 | 70/2758 | 2.5 |
| Pediatric Oncohematology | 1/86 | 1.2 | 7/109 | 6.4 | 8/195 | 4.1 |
| Internal Medicine | | | | 7.9 | 41/533 | 7.7 |
| ICU | | | | 11.9 | 26/165 | 15.7 |
| Pneumology | | | | 16.2 | 7/87 | 8 |
| COVID | | | | 5.8 | 166/2856 | 5.8 |
| Outpatients | | | | 17.6 | 8/46 | 17.4 |
| Infectious Diseases | | | | 6.9 | 6/131 | 4.5 |
| Surgery | | | | 21.3 | 12/67 | 17.9 |
| Other Specialties | | | | 9.2 | 18/220 | 8.2 |
| Outpatient Hospital | 3/41 | 1.5 | 11/63 | 17.5 | 14/104 | 12.5 |
| Total | 54/1902 | 2.8 | 322/5260 | 6.1 | 376/7162 | 5.2 |

**Sonuçta; CAPA artış** mevcut

**Riskler**;

✓**immünosüpresyon**,

✓non-invazif **ventilasyon**,

✓oro-trakeal **entübasyon**

✓yüksek doz **kortikosteroid**

*Int J Environ Res Public Health*. 2022; 19: 7079.

Journal of Fungi

*J Fungi*. **2023**; 9: 131

*Review*

# Invasive Pulmonary Aspergillosis

Marie-Pierre Ledoux * and Raoul Herbrecht

Global olarak **≈10 mlyn risk altındaki** hasta için tahmini insidans;

**İA** için; > **300 000**

**Kronik PA** için ≈**3 000 000**

**Alerjik BPA** için ≈**4 800 000**

- **ICU mortality** reaches **45%** in **Influenza APA** compared with **20% influenza alone.**

➢Farklı çalışmalardan;

**İA >%85**'i hematolojik maligniteli veya alloKİT veya SOT hastalarında

**CAPA;** Risk faktörler;

**Yaş> 62**, **deksametazon** ve **anti-IL6 kullanımı**, **<14 gün** mekanik ventilasyon

**Ölüm** hazard oranı **1.45 CAPA** hastalarında, olmayanlara göre

**Soru(n) 2**

**İA tanısında** kullanılan **standard yöntemlerin** halen bir rolü var mı?

*Clinical Infectious Diseases* **2019**.

MAJOR ARTICLE

# 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

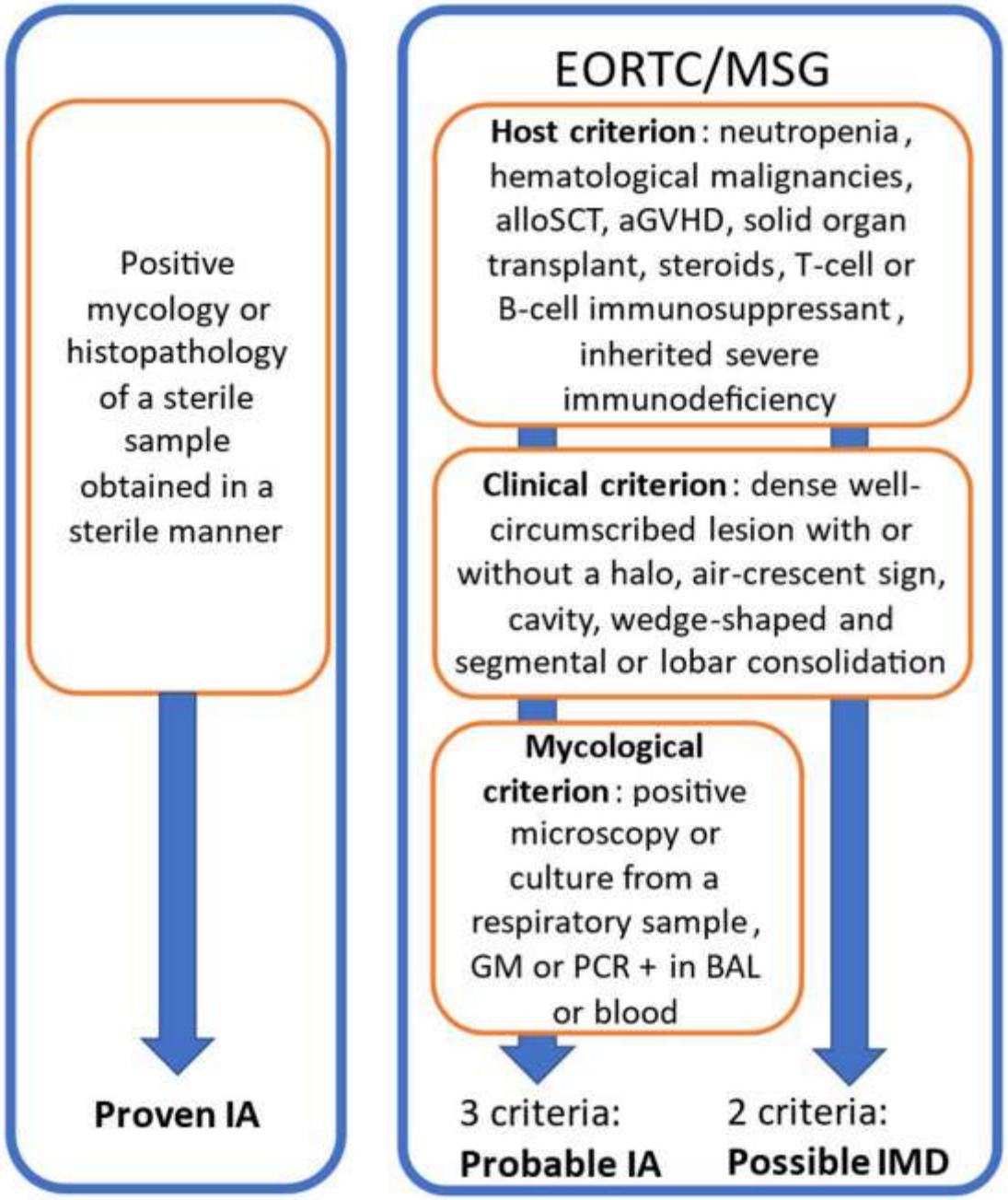
*Clinical Infectious Diseases*

SUPPLEMENT ARTICLE

# EORTC/MSGERC Definitions of Invasive Fungal Diseases: Summary of Activities of the Intensive Care Unit Working Group

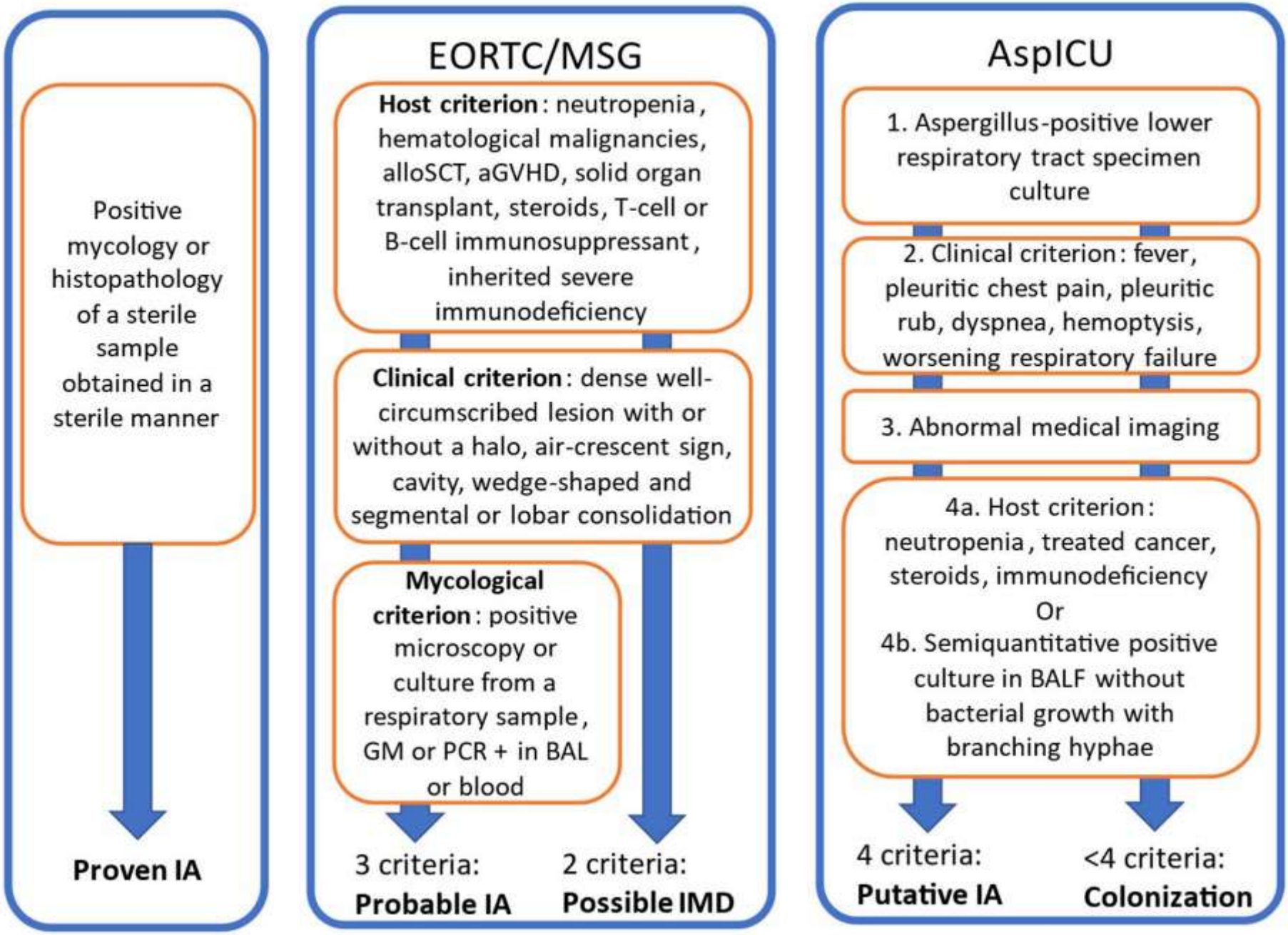
Matteo Bassetti,[1,2] Elie Azoulay,[3,4] Bart-Jan Kullberg,[5] Markus Ruhnke,[6] Shmuel Shoham,[7] Jose Vazquez,[8] Daniele Roberto Giacobbe,[1] and Thierry Calandra[9]

Clinical Infectious Diseases® 2021;72(S2):S121–7




BALF, bronchial brush or aspirate, or **GM** detected in **blood ≥ 1.0**, or in **BALF ≥ 1.0** or **both blood ≥ 0.7** and **BALF ≥ 0.8,**
or a **PCR** positive in blood **twice** or in BALF twice (first analysis and duplicate) or once in both blood and BALF.

*J Fungi*. 2023; 9: 131




*J Fungi*. 2023; 9: 131

| Criteria | | Clinical | Radiological | Mycological |
|---|---|---|---|---|
| EORTC/MSGERC (1) | **Proven IPA** | - | - | **Lung biopsy**, at least 1:<br>• Histo/cytopathologic or direct microscopic examination (hyphae + tissue damage)<br>• Positive culture from tissue |
| | **Probable IPA** | **Host factors**:<br>Neutropenia, malignant hemopathy, transplant, prolonged corticosteroids (>0.3mg/kg >3weeks/2months), immunosuppressive drugs… | **CT pattern**, at least 1:<br>• Dense, well-circumscribed lesion (±halo)<br>• Air crescent sign<br>• Cavity<br>• Consolidation | At least 1:<br>• Positive direct microscopy or culture of a respiratory sample (sputum, tracheal aspirate, BAL)<br>• BAL GM ≥1<br>• Serum GM ≥1<br>• BAL GM ≥0.8 and serum GM ≥0.7<br>• Positive *Aspergillus* PCR *x2* (serum or BAL) |
| | **Possible IPA** | *Same as probable IPA* | *Same as probable IPA* | - |
| *Asp*ICU (2) | **Proven IPA** | - | - | *Same as EORTC/MSGERC* |
| | | ***Entry criterion: Positive culture of lower respiratory tract specimen*** | | |
| | | **Compatibles signs/symptoms:**<br>Fever despite antibiotics >3d or recrudescent after 48h defervescence, dyspnea, hemoptysis, chest pain, pleuritic rub, worsening respiratory insufficiency | **Chest X-ray or CT scan:**<br>Abnormal imaging (any infiltrate) | **In the absence of host risk factor:**<br>Positive direct microscopy (hyphae) and culture of BAL |
| | | **± Host risk factors:**<br>Neutropenia, chemotherapy, corticosteroids>20mg/d, congenital or acquired immunodeficiency | | |
| | ***Aspergillus* colonization** | ≥1 criterion for putative IPA is not met | | |

Kabul edilen

*Curr Opin Crit Care*. 2022, 28:470-9.

EORTC/MSGERC; European Organization Treatment of Cancer and the Mycoses Study G.

# Tanı Yöntemlerinin Kıyaslanması

| Diagnostic Methods | Advantages | Disadvantages |
|---|---|---|
| Histopathology and microbiology | Gold standard<br>Pathologic changes of the tissue<br>Morphology of the *Aspergillus* | Invasive operation<br>High requirements for specimen quality<br>Technology dependent on the technician<br>Time-consuming<br>False-negative |
| Fungal biomarker assay | Early detection<br>Non-invasive<br>Various sample resources<br>Platform widely available<br>Rapid turnaround time | False-positive<br>False-negative<br>Unknown pathogen species<br>Unknown infection site |
| *Aspergillus* polymerase chain reaction (PCR) test | Specific species<br>Various sample resources<br>Rapid turnaround time | Lack of standardization<br>Contamination can be problematic |
| CT scanning | Fast and non-invasive<br>Location of infection site<br>Lesion size and number | Non-specific<br>Pathogen not identified<br>Viability of pathogen not indicated |
| Serological antibody test | Easily performed on readily accessible samples | False-negative in immunocompromised host |

*Int J Mol Sci*. **2022**; 23: 5563.

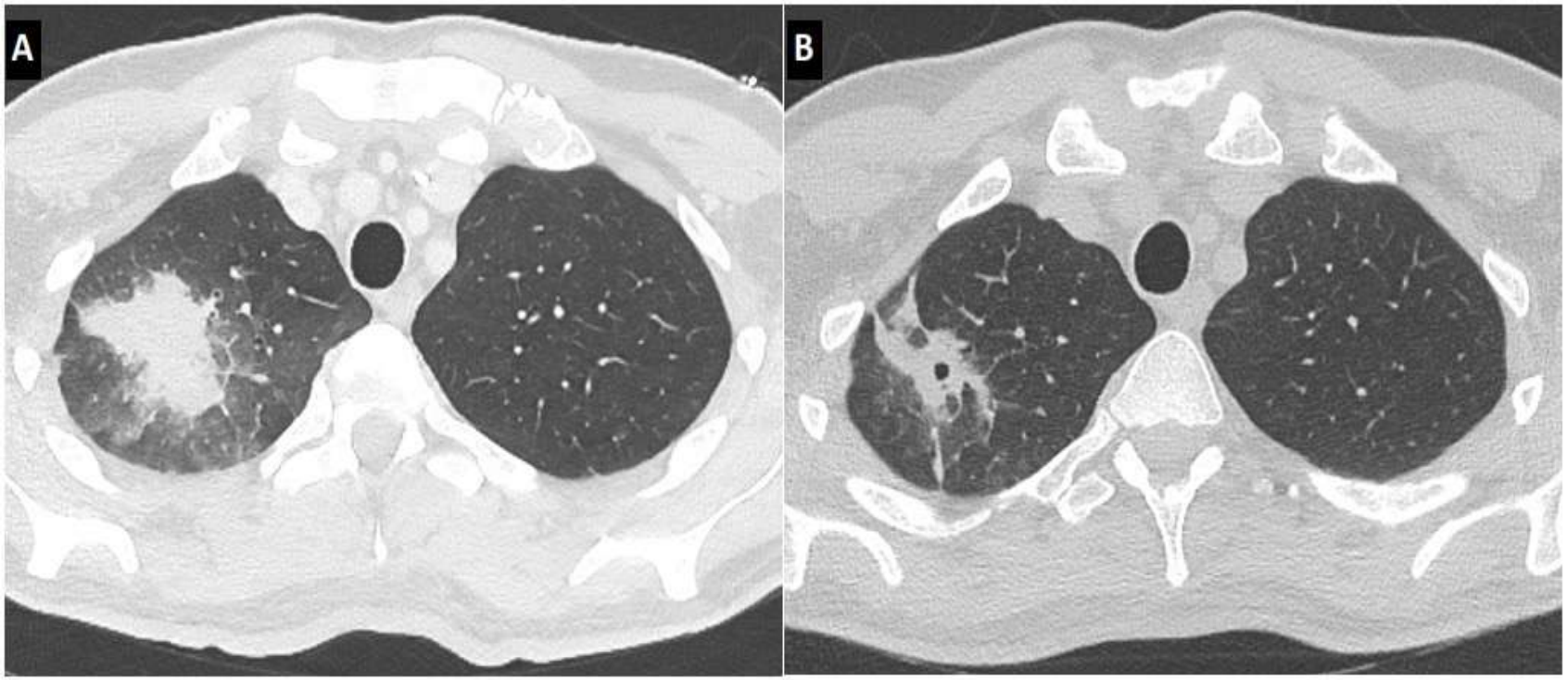
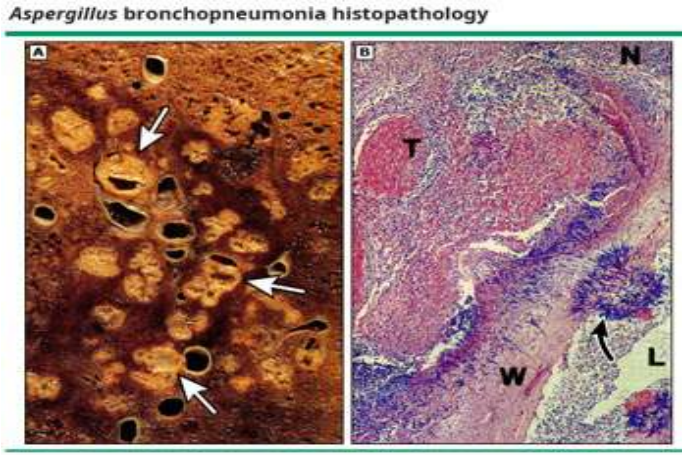



**Figure 1.** Invasive aspergillosis in a refractory acute myeloblastic leukemia patient. (**A**) CT-scan at diagnosis, showing a nodule surrounded by a halo. (**B**) CT-scan 4 weeks later, showing a small cavity.




*J Fungi*. 2023; 9: 131

International Journal of
*Molecular Sciences*

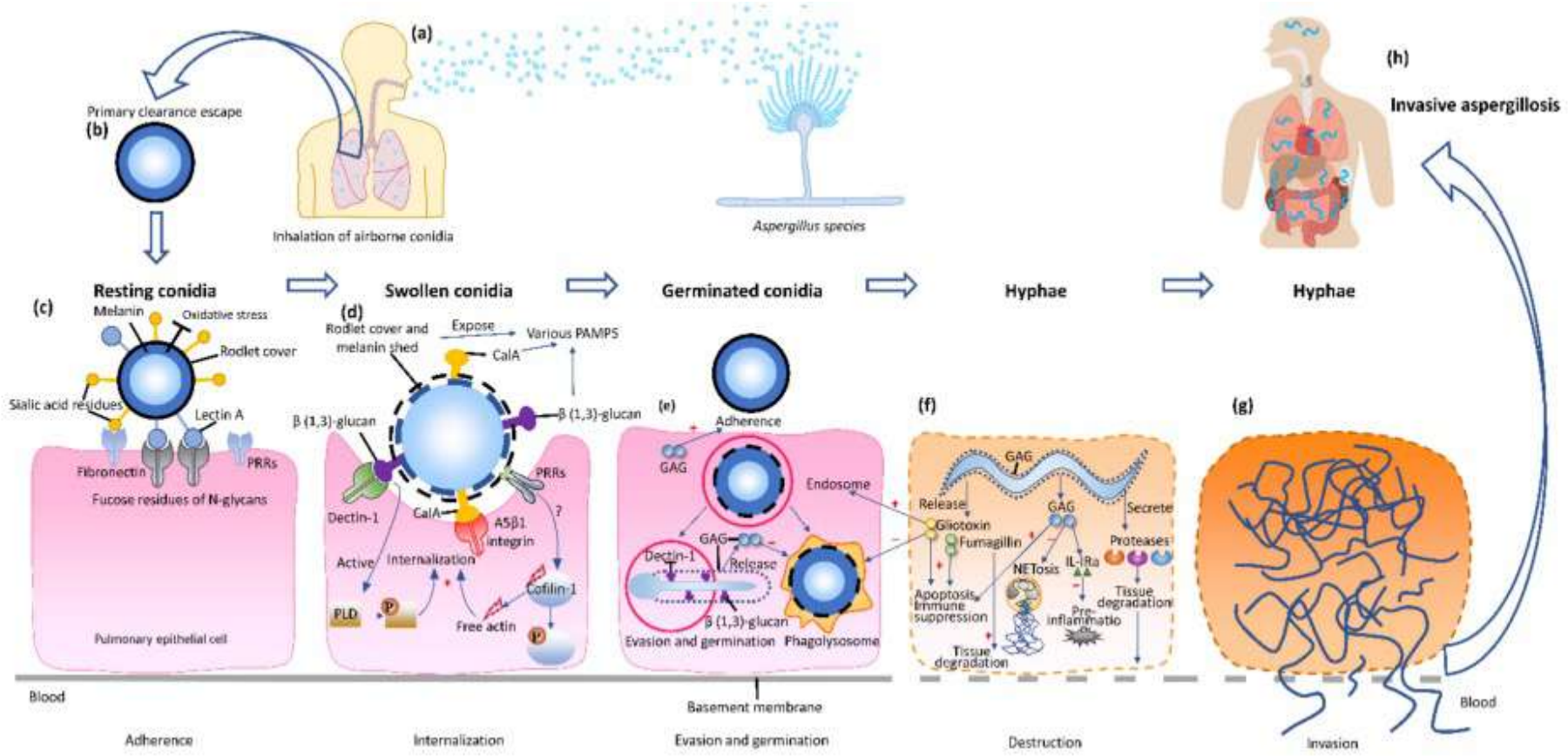
*Int J Mol Sci*. **2022**; 23: 5563.

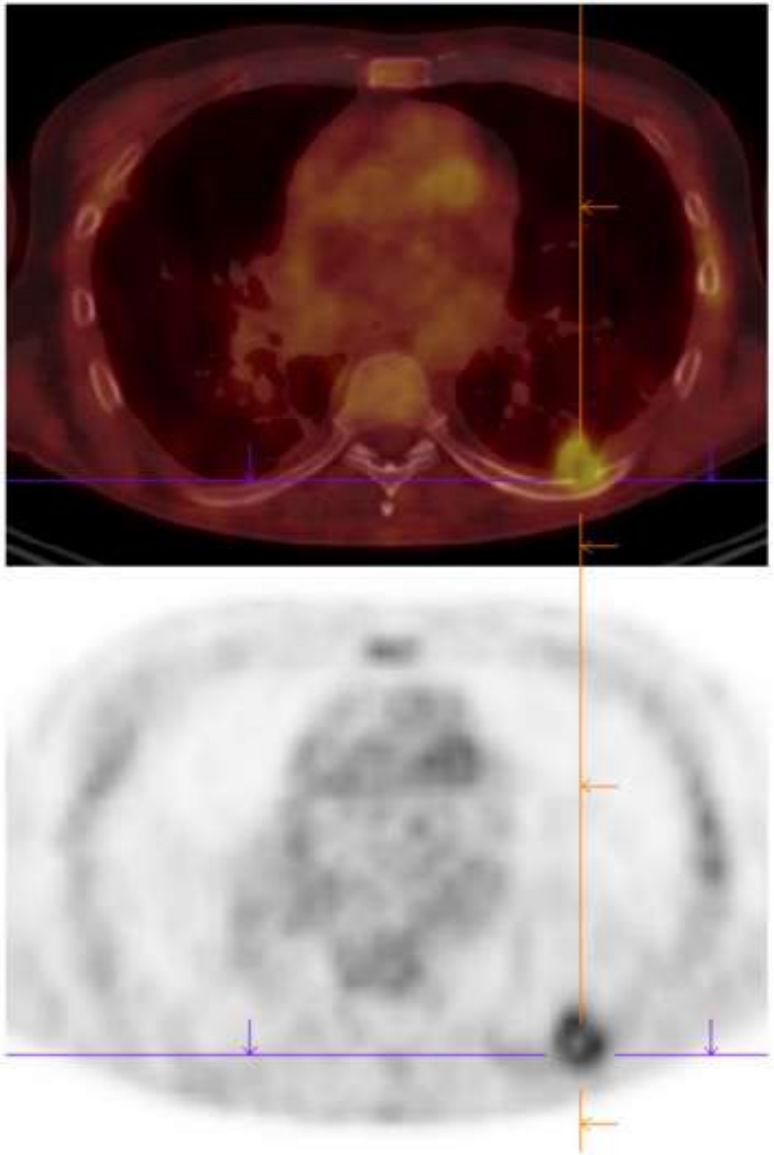
MDPI

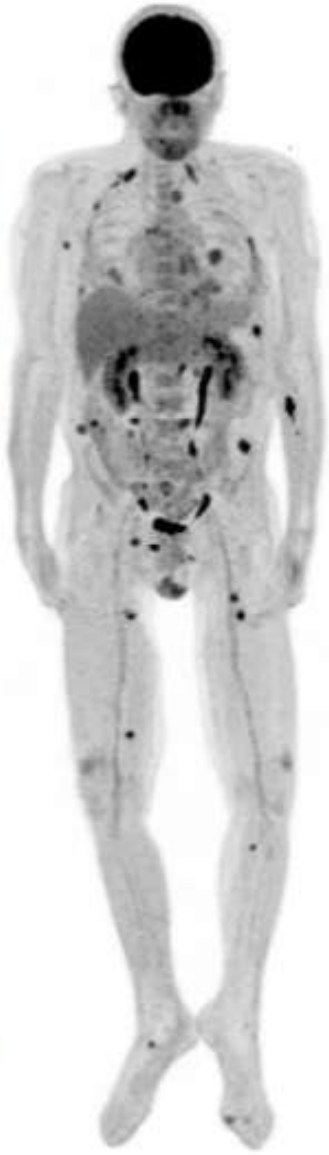
*Review*

# Monoclonal Antibodies and Invasive Aspergillosis: Diagnostic and Therapeutic Perspectives

**Xihua Lian [1,2,†], Amy Scott-Thomas [1,†], John G. Lewis [1,3], Madhav Bhatia [1], Sean A. MacPherson [1,4], Yiming Zeng [5] and Stephen T. Chambers [1,*]**







**Immune**

**PET/MRI** ile

görüntülenebilir

**Figure 3.** Positron-emission tomography coupled with CT-scan in invasive aspergillosis

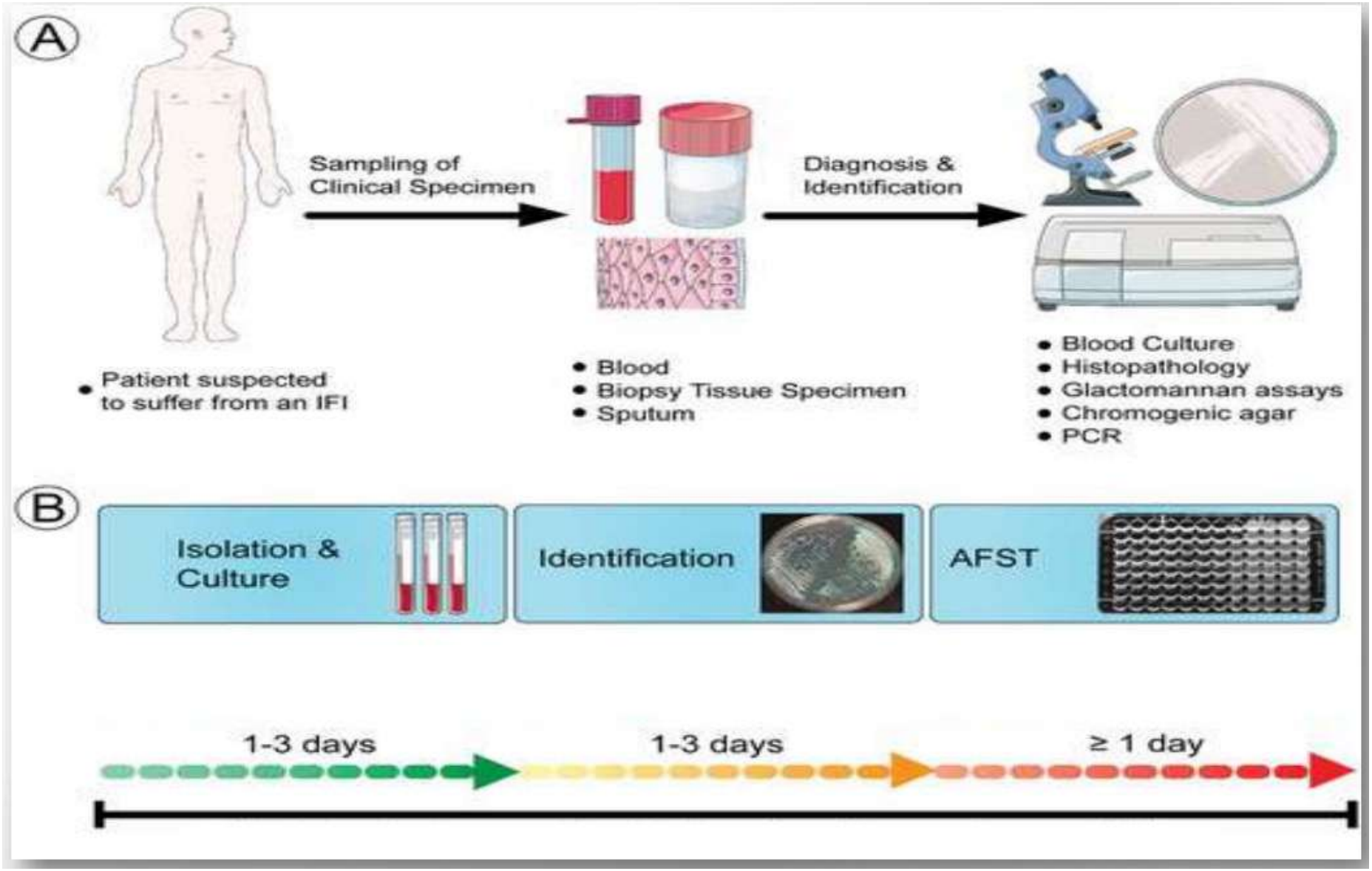
*J Fungi*. 2023; 9: 131

**Soru(n) 3 / 4**

**3.** İA yönetiminde **antifungal duyarlılık testlerinin rolü nedir?**

**4. Azol direnci sorun mu?**

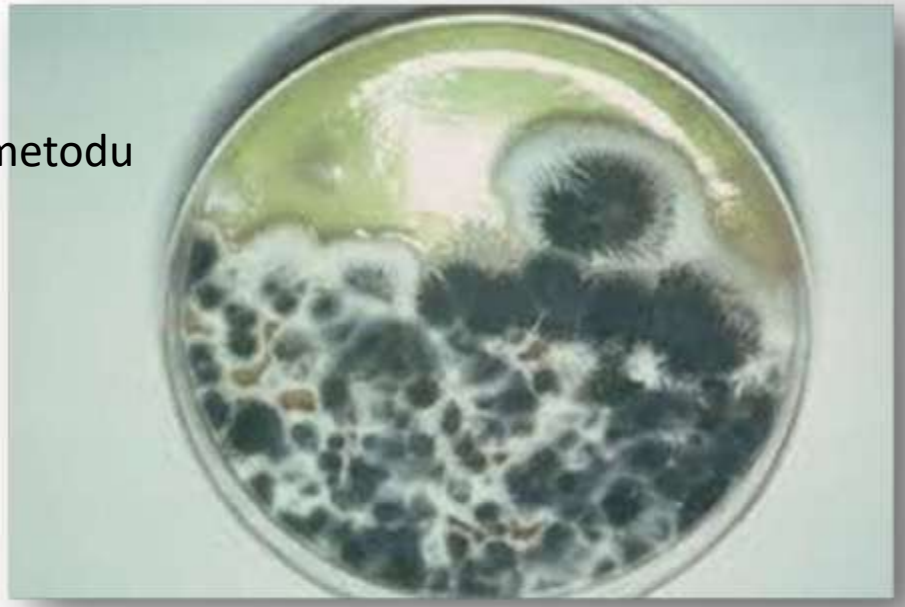
**Tanı;**

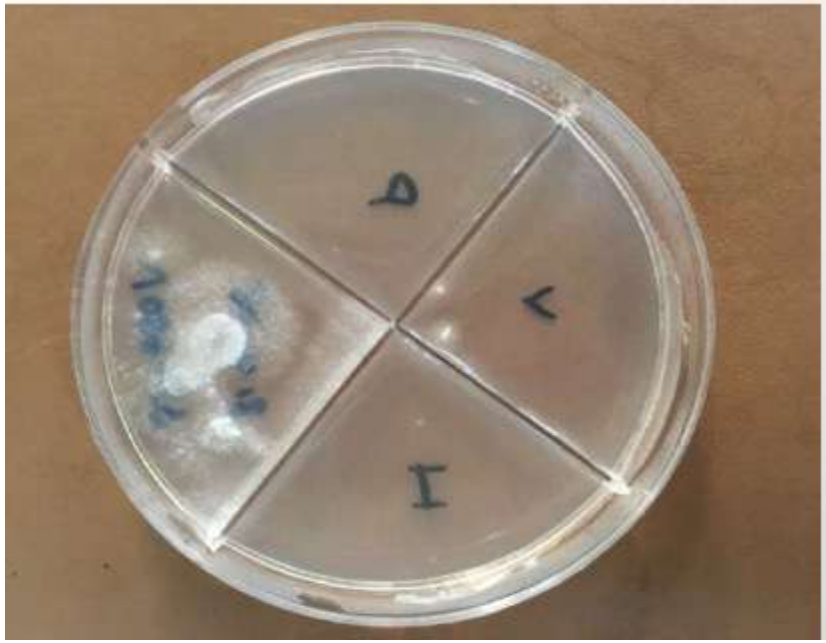



**İA** olgularının önemli bir kısmı **kültür dışı yöntemlerle** belirleniyor

**Antifungal duyarlılık**

EUCAST **agar tarama** metodu



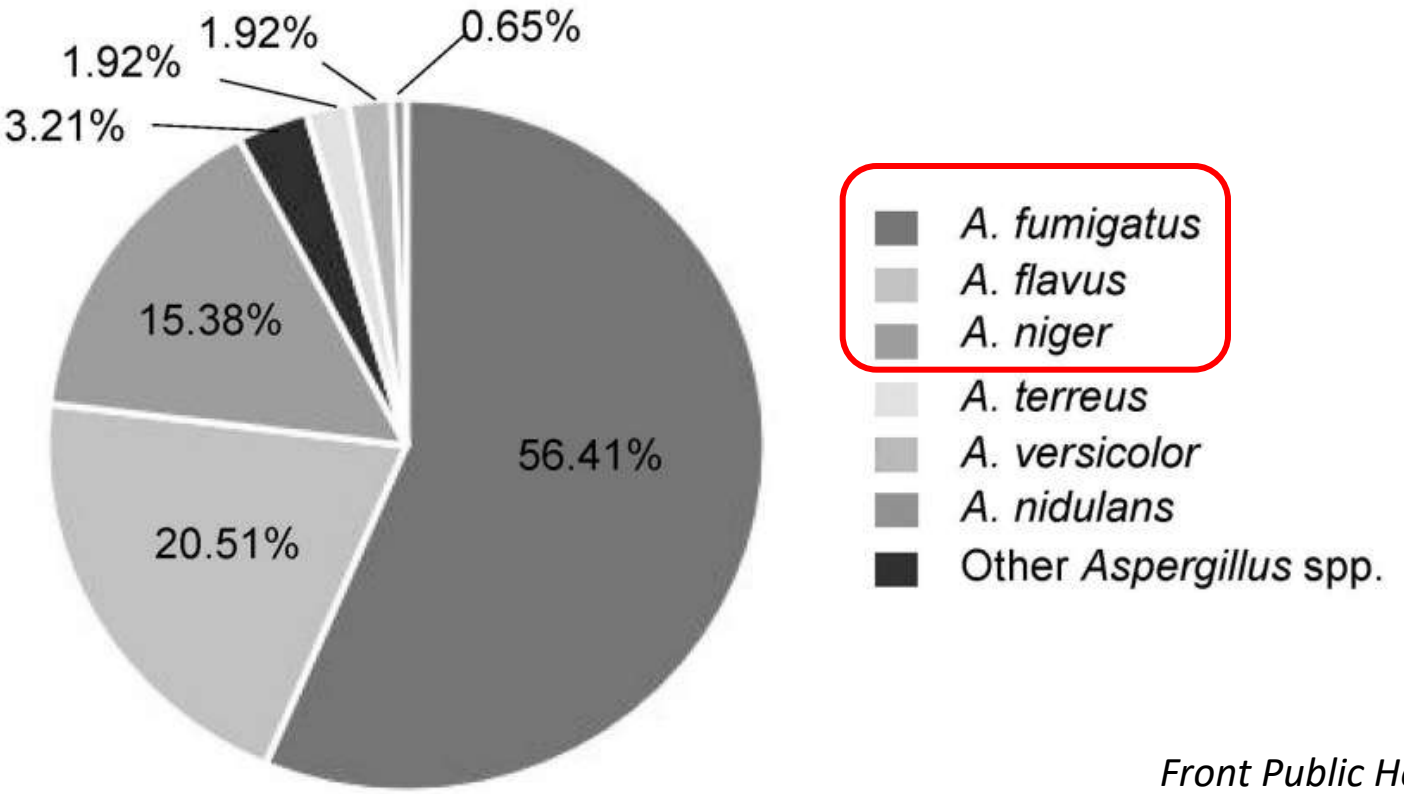


# Epidemiology, Drug Susceptibility, and Clinical Risk Factors in Patients With Invasive Aspergillosis

Frontiers in Public Health

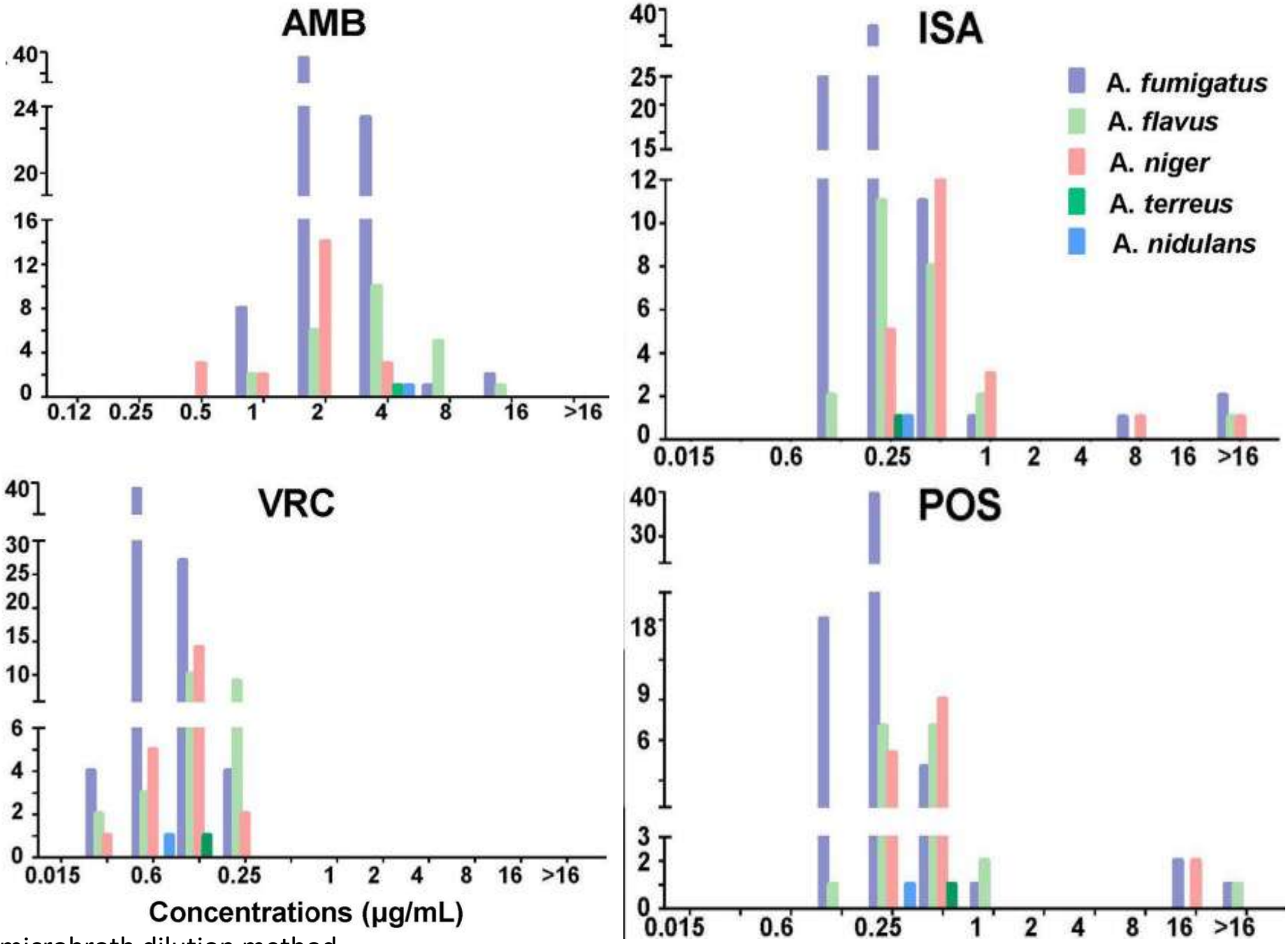
*Yuerong Wang, Luwen Zhang, Longrong Zhou, Min Zhang* and Yuanhong Xu**

Çin, **2800** yataklı hastane, **2019-2021** toplam **156** ***Aspergillus*** spp. isolatı





*Front Public Health*. 2022; 10: 835092




microbroth dilution method

## Sonuç olarak;

İnt R hariç **AmfB direnci**; **MIC> 2µg/ml**

*A. fumigatus* → **%39.7** (29/73)

*A. flavus* → **%54.1** (13/24)

*A. niger* → **%13.6** (3/22)

***A. fumigatus*** için **cyp51A** gen polimorfizmi **TR46/Y121F/T289A** mutasyonu **azol direncine sebep ve İA** hastalarında tedavi başarısızlıklarına katkıda bulunur

***Aspergillus* spp.**

- ✓ **Flusitozin** için **yüksek MIC >64µg/ml** (*A.niger* hariç)
- ✓ Mikafungin MIC ≤0.008 to 0.02µg/ml
- ✓ Caspofungin MIC ≤0.008 to 0.03µg/ml
- ✓ **Posakonazol MIC ≤0.5µg/ml** (n = 120, **%99.1**) (***A. fumigatus* %100** duyarlı)
- ✓ **VRC** duyarlılığı n = 110, **%90.9** (***A. fumigatus* %95.8** duyarlı)
- ✓ **ISA** duyarlılığı n = 107, **%88.4** (***A. fumigatus* %95.8** duyarlı)

*Front Public Health*. 2022; 10: 835092

# First determination of azole resistance in *Aspergillus fumigatus* strains carrying the TR34/L98H mutations in Turkey

*J Infect Chemother* **2015**;21:581e6.

Gülşah Ece Özmerdiven, Seçil Ak, Beyza Ener, Harun Ağca, Burcu Dalyan Cilo, Berrin Tunca, Halis Akalın

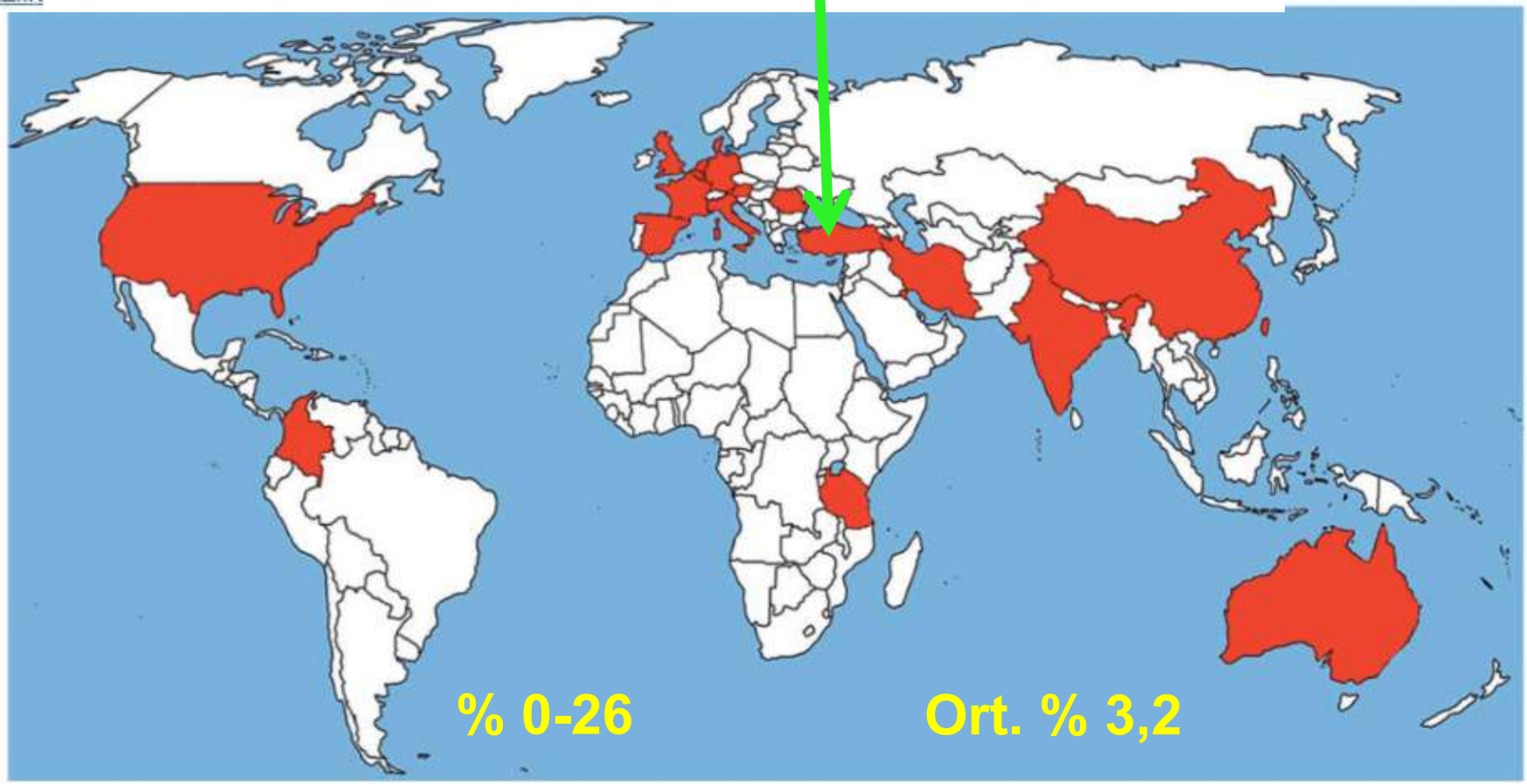



**Figure 1.** Shaded areas show countries that have reported the $TR_{34}$/L98H and $TR_{46}$/Y121F/T289A resistance mechanism in clinical or environmental *Aspergillus fumigatus* isolates.

**Mortalite** infekte olan & olmayan **%88** vs. **30–50**.

*J Antimicrob Chemother* 2022; **77**: 1894–1898
https://doi.org/10.1093/jac/dkac125 Advance Access publication 21 April 2022

Journal of Antimicrobial Chemotherapy

# Frequency of azole resistance in clinical and environmental strains of *Aspergillus fumigatus* in Turkey: a multicentre study

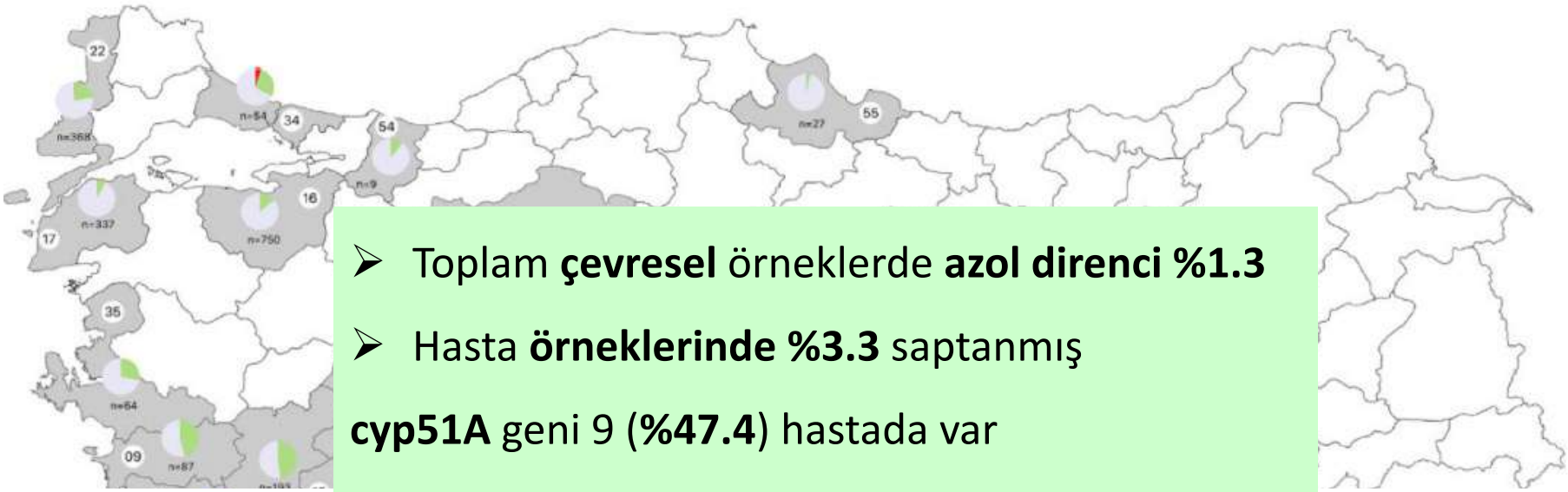
**Beyza Ener[1]*, Çağrı Ergin[2], Dolunay Gülmez[3], Harun Ağca[1], Melek Tikveşli[4], Seçil Ak Aksoy[5], Müşerref Otkun[6], Ali Korhan Sığ[3], Dilara Öğünç[7], Betil Özhak[7], Tuncay Topaç[8], Aslı Özdemir[6], Dilek Yeşim Metin[9], Süleyha Hilmioğlu Polat[9], Yasemin Öz[10], Nedret Koç[11], Mustafa Altay Atalay[11], Zayre Erturan[12], Asuman Birinci[13], Nilgün Çerikçioğlu[14], Demet Timur[1], Fahriye Ekşi[15], Gonca Erköse Genç[12], Duygu Findik[16], Şaban Gürcan[4], Ayşe Kalkanci[17] and Sevtap Arikan-Akdagli[3]**

1 May **2018** -1 Ekim **2019**

Toplam **21 merkez**

**Azol direnci** EUCAST **agar tarama** metodu (EUCAST E.DEF 10.1) doğrulaması da EUCAST E.DEF 9.3 referans **mikrodilüsyon**

**Fenotipik** direnci sekans **cyp51A** geni ve mikrosatellit genotiplendirme yapılmış.




- Toplam **çevresel** örneklerde **azol direnci %1.3**
- Hasta **örneklerinde %3.3** saptanmış

**cyp51A** geni 9 (**%47.4**) hastada var

**Sonuç:**

«**Azole resistance** of ***A. fumigatus*** isolates was **low** in this study»

| Isolate | City code | | | | | *cyp51A* mutation |
|---|---|---|---|---|---|---|
| ÇK1 | 34 | | | | | none |
| CRK1 | 34 | | | | | none |
| CRK2 | 34 | | | | | none |
| 011KS06SN-B1 | 06 | | | | | none |
| 011KS06SN-B2 | 06 | | | | | none |
| 267MT22MR/B | 22 | agricultural soil | - | 4 | 4 | 2 | none |
| 60986 | 16 | sputum | 45 | >8 | >8 | 2 | TR34/L98H |
| 61568 | 16 | sputum | 63 | >8 | >8 | 2 | TR34/L98H |
| 62946 | 16 | bronchoalveolar lavage fluid | 81 | >8 | >8 | 2 | TR34/L98H |
| 63413 | 16 | sputum | 74 | >8 | >8 | 2 | TR34/L98H |
| 63653 | 16 | tracheal aspirate | 67 | >8 | >8 | 2 | TR34/L98H |
| 64955 | 16 | bronchoalveolar lavage fluid | 80 | >8 | >8 | 2 | TR34/L98H |
| 2455 | 06 | pleural fluid | | >8 | >8 | 2 | TR34/L98H |
| 457 | 06 | pus | | >8 | >8 | 2 | TR34/L98H |
| MY | 27 | bronchoalveolar lavage fluid | | 2 | 2 | 0.5 | TR34/L98H |
| RT1 | 34 | sputum | 75 | 4 | 4 | 0.5 | none |
| RT2 | 34 | sputum | 75 | 4 | 4 | 0.5 | none |
| 11b | 07 | sputum | 18 | 4 | 4 | 2 | none |
| 13b | 07 | sputum | 54 | >8 | 4 | 2 | none |

*J Antimicrob Chemother* 2022; 77: 1894–8.

# *Aspergillus fumigatus*'da Azol Direnci

- 14 α-demetilaz enzimini kodlayan *cyp51 A* geninde mutasyon
  - G54 kodonunda mutasyon
    - İtrakonazol ve Posakonazol direnci
  - M220 kodonunda mutasyon
    - Tüm azoller
  - G448 kodonunda mutasyon
    - Vorikonazol

Azollerin uzun süre kullanılması

- TR34/L98H mutasyonu
  - Tüm azoller
- TR46/Y121F/T289A
  - Vorikonazol

- Zirai azol birleşikleri
  - Gıdaların korunmasında
  - Bitkilerin korunmasında
  - Eşya korunmasında
- Azol naif kişileri de enfekte edebilir

Prof. Dr. B.Ener'in izniyle

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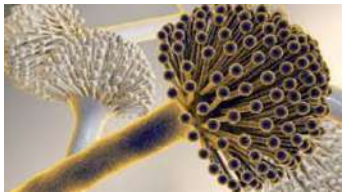
# İnvazif Fungal İnfeksiyon Yönetimi


I. 2016 IDSA

II. 2017 ECIL-6

III. ESCMID (Küfler 2018)

IV. Yeni çalışmalar



Lancet Infect Dis 2020

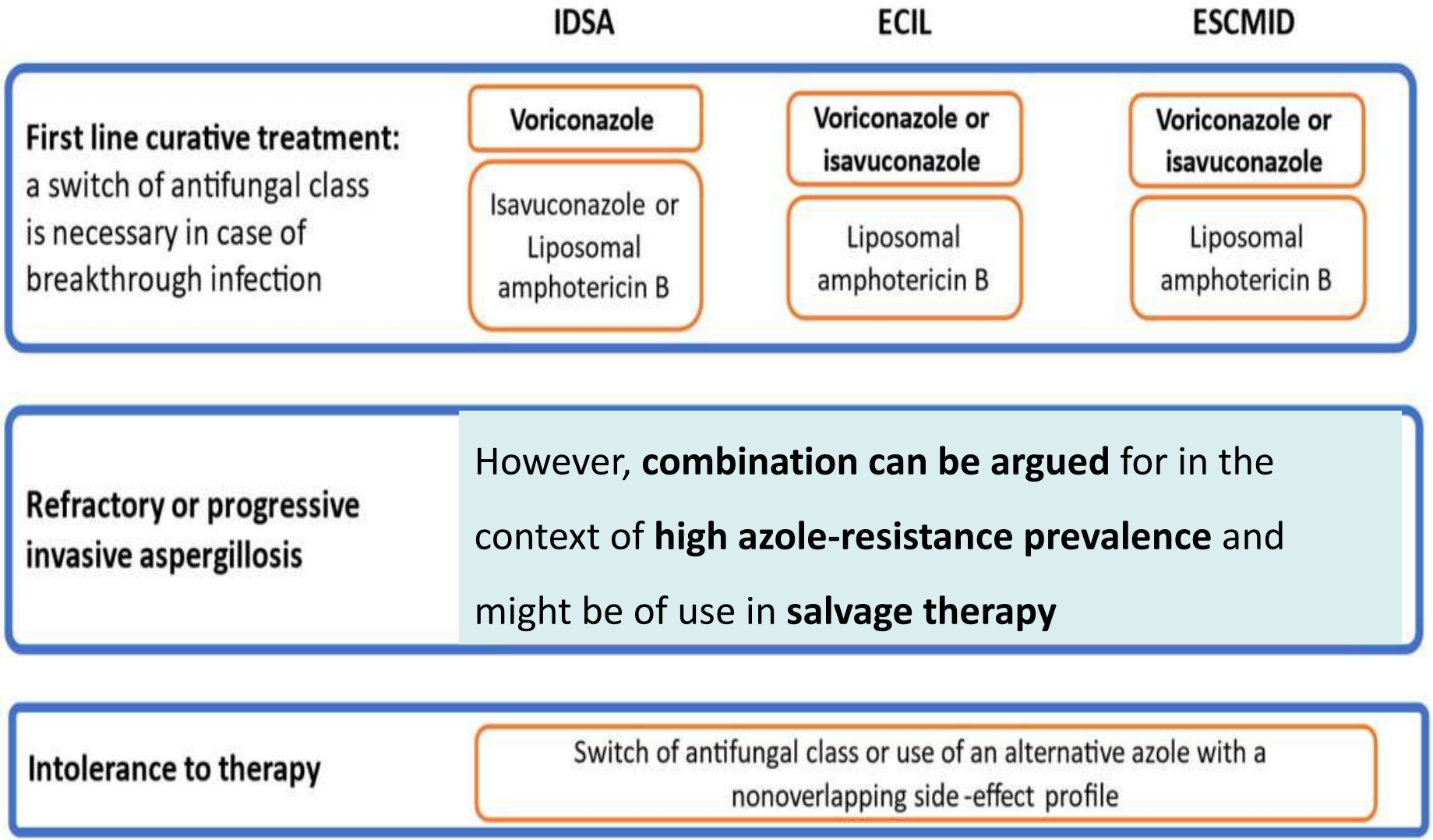
**Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance**

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

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

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

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




IDSA. *J Fungi Basel*. 2019
ECIL-6. *Haematologica*. 2017
ESCMID. *Clin Microbiol Infect*. 2018

*J Fungi*. 2023; 9: 131

# *A.fumigatus*-Azol direnci

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

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

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 |

In settings with **environmental azole resistance**, **no change to the primary regimen** for IA is recommended when resistance rates are **<10%** (AIII).

If azole **resistance rates are >10%,** first-line therapy with **voriconazole plus echinocandin** (BIII) or **liposomal amphotericin B** (BIII) is recommended.

# Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021

**Table 5** Recommendations for first-line therapy against invasive pulmonary aspergillosis in adults

| Medication | Dosage | SoR | QoE | Notes |
|---|---|---|---|---|
| First-line | | | | |
| Voriconazole | IV: 6 mg/kg twice daily on day 1, then 4 mg/kg IV twice daily<br>Oral: 4 mg/kg twice daily | A | I | • Caution if already on triazole prophylaxis<br>• TDM strongly recommended |
| Second-line or alternative options | | | | |
| Isavuconazole | IV or oral: 200 mg three times daily for six doses, then 200 mg daily | A | I | • Caution if already on triazole prophylaxis |
| Posaconazole | IV or oral tablet: 300 mg twice daily day 1, then 300 mg daily<br>Oral suspension: 400 mg twice daily, or 200 mg four times daily if unable to take with food | A | I | • TDM recommended |
| Liposomal amphotericin B | IV: 3 mg/kg daily | B | II | • Where there is breakthrough infection on azole therapy/ prophylaxis<br>• In drug–drug interaction settings with azoles |

*Internal Medicine J*. 2021; 51(S7): 143-76.

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

*Johan A Maertens, Galia Rahav, Dong-Gun Lee, Alfredo Ponce-de-León, Isabel Cristina Ramírez Sánchez, Nikolay Klimko, Anne Sonet, Shariq Haider, Juan Diego Vélez, Issam Raad, Liang-Piu Koh, Meinolf Karthaus, Jianying Zhou, Ronen Ben-Ami, Mary R Motyl, Seongah Han, Anjana Grandhi, Hetty Waskin, on behalf of the study investigators**

**Metod**

**Posakonazol & Vorikonazol** karşılaştırması yapılan, randomize, prospektif, çift kör kontrollü bir çalışma

**Posakonazol** 300 mg 1. gün 2x1 İV veya oral, ardından 2-84. günler 1x300 mg

**Vorikonazol** 1. günde 2x6 mg/kg İV veya oral, ardından 2x4 mg/kg İV veya 2x200 mg

*Lancet*. 2021; 397: 499–509

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

| | Posaconazole group | Voriconazole group | Treatment difference (95% CI)* | p value |
|---|---|---|---|---|
| **All-cause mortality** | | | | |
| ITT population | | | | |
| Day 42 all-cause mortality† | 44/288 (15%) | 59/287 (21%) | −5·3% (−11·6 to 1·0)‡ | <0·0001§ |
| Day 84 all-cause mortality | 81/288 (28%) | 88/287 (31%) | −2·5% (−9·9 to 4·9) | NA |
| **Global clinical response in the FAS population** | | | | |
| Success at week 6 | 73/163 (45%) | 78/171 (46%) | 0·6% (−11·2 to 10·1) | NA |
| Complete response¶ | 11/163 (7%) | 9/171 (5%) | .. | .. |
| Partial response‖ | 62/163 (38%) | 68/171 (40%) | .. | .. |
| Stable response, progression of fungal disease, death, or unable to assess at week 6 | 90/163 (55%) | 93/171 (54%) | .. | .. |
| Stable response** | 12/163 (7%) | 22/171 (13%) | .. | .. |
| Progression†† | 27/163 (17%) | 21/171 (12%) | .. | .. |
| Death | 34/163 (21%) | 33/171 (19%) | .. | .. |
| Unable to assess | 17/163 (10%) | 17/171 (10%) | .. | .. |
| Success at week 12 | 69/163 (42%) | 79/171 (46%) | −3·4% (−13·9 to 7·1) | NA |
| Complete response¶ | 20/163 (12%) | 19/171 (11%) | .. | .. |

*Lancet*. 2021; 397: 499–509

ITT=intention-to-treat. NA=not assessed. FAS=full analysis set.

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

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- ✓ **Posakonazol,** katılımcılarda 42. güne kadar tüm nedenlere bağlı ölümlerde vorikonazolden daha aşağı değildir.
- ✓ İnvazif aspergilloz tedavisinde posakonazol **iyi tolere edildi** ve katılımcılar **daha az tedaviyle ilişkili yan etki** yaşadı.

Bu çalışma, **posakonazolün birinci basamak tedavi** olarak **kullanılmasını desteklemektedir.**

*Lancet*. 2021; 397: 499–509

Sorumlu klinisyen tarafından **İA** olarak kabul edilen risk altındaki herhangi bir hasta antifungal tedavi almalıdır **(AIII).**

**İnvazif Aspergilloz Tedavi Süresi**

- En az **6- 12** hafta
- İnfeksiyonun lokalizasyonu
- Klinik iyileşme
- Alta yatan hastalığın iyileşmesi
- Nötropeni süresine
- Saptanan lezyonlar tamamen kaybolana ya da skar halini alana kadar

Aspergillosis. IDSA Guideline *CID.* 2016:63

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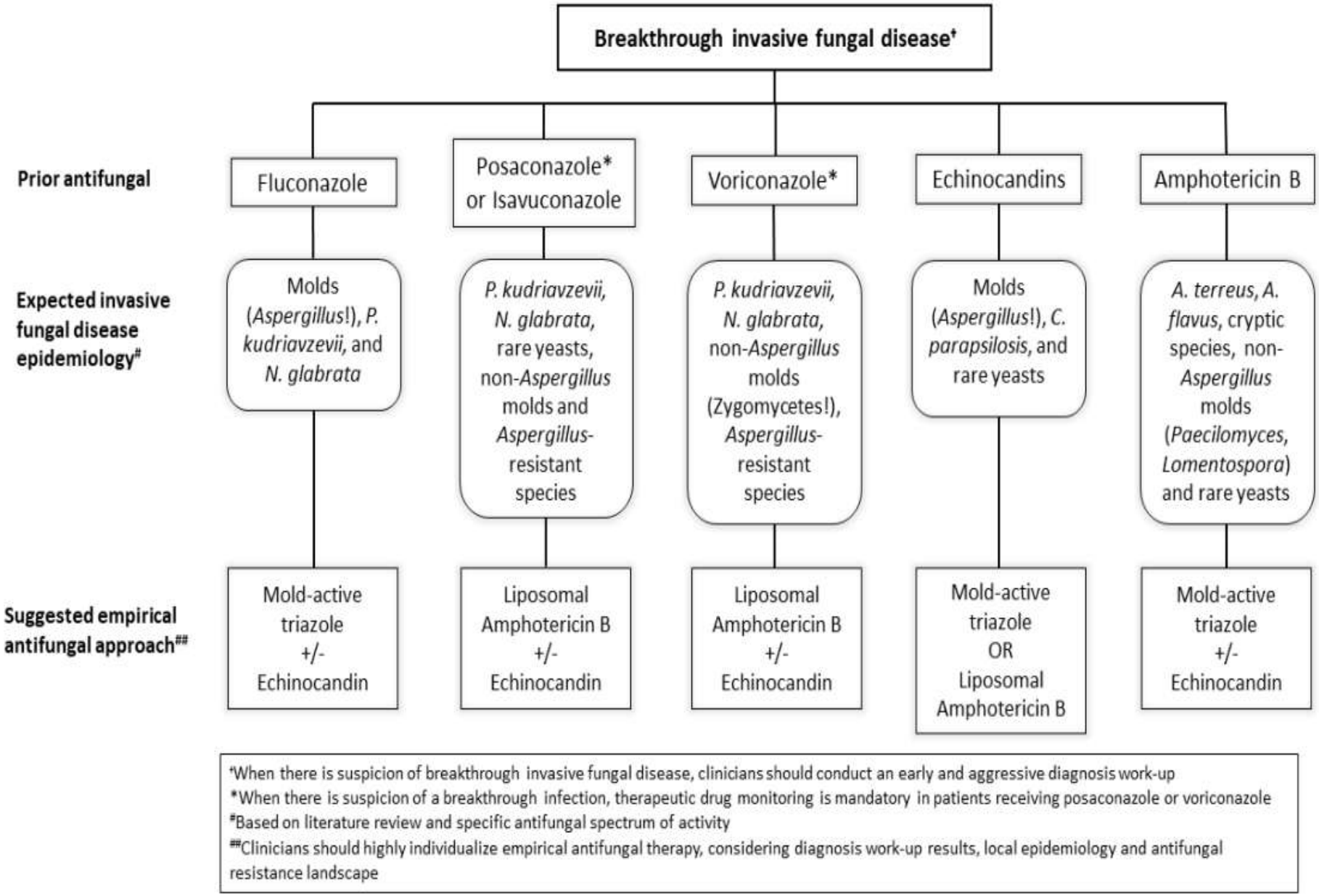
**Soru(n) 5**

**‘Breakthrough’ IA nedir** ve nasıl

**yönetilmelidir?**

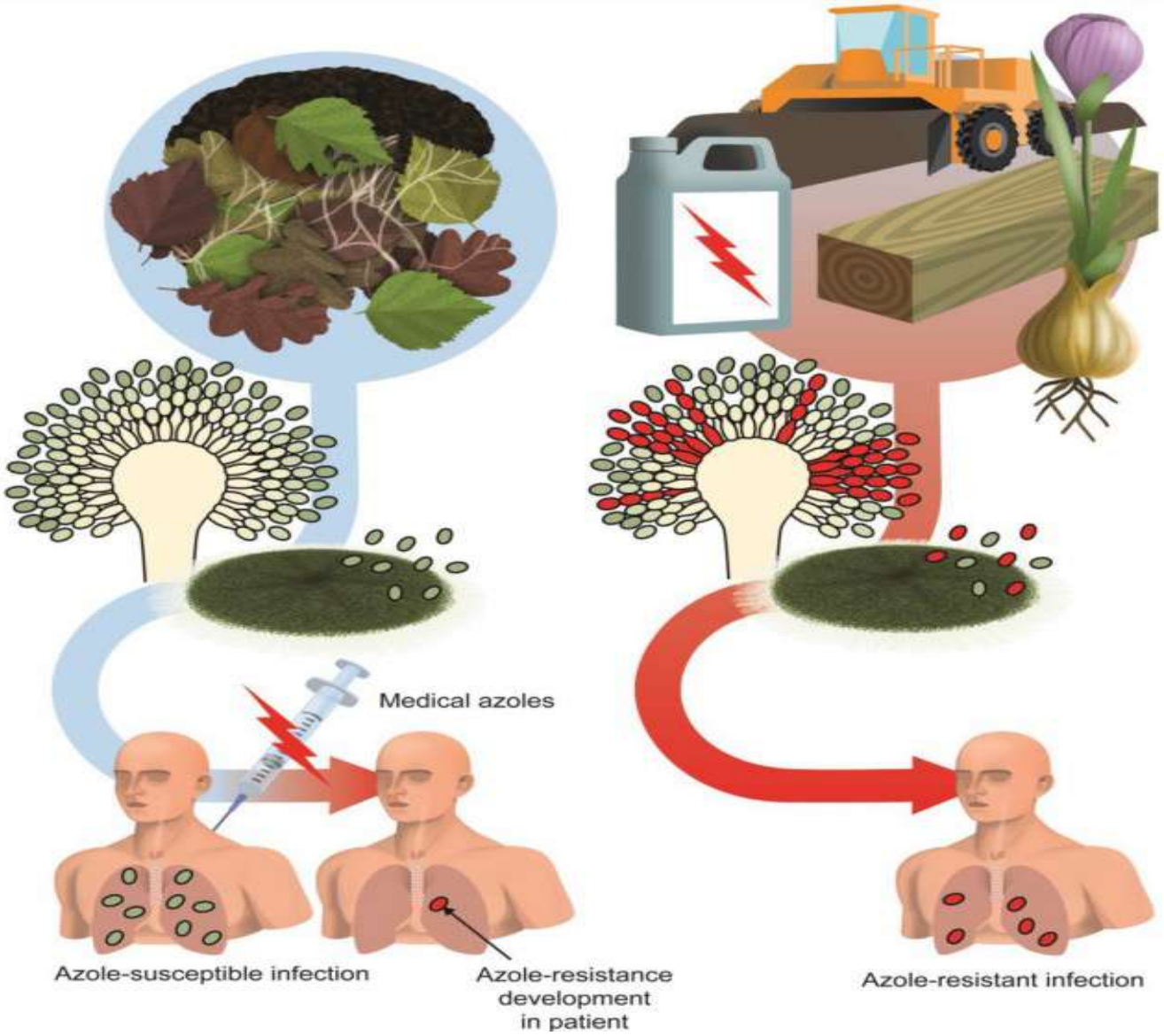



†When there is suspicion of breakthrough invasive fungal disease, clinicians should conduct an early and aggressive diagnosis work-up
*When there is suspicion of a breakthrough infection, therapeutic drug monitoring is mandatory in patients receiving posaconazole or voriconazole
#Based on literature review and specific antifungal spectrum of activity
##Clinicians should highly individualize empirical antifungal therapy, considering diagnosis work-up results, local epidemiology and antifungal resistance landscape

Puerta-Alcalde P, *et al*. Changing Epidemiology. *J Fungi*. **2021**; 7: 848.

British Mucological


Check for updates




20: 34: 202-14.

## Özetle;

- **İFİ**'ler immünokompromize konakta **hayatı tehdit eder**
- Ülkemizde en büyük eksiklik **epidemiyolojik verinin** olmaması
- Her **merkezin kendi epidemiyolojik verisini** oluşturması gerekir
- Tanısında daha iyi **görüntüleme** ve **yeni biyobelirteç** sayesinde tanı hızlanmakta
- **Küfler için antifungal duyarlılık** testleri zaman alıcı (**7-10 gün**), **tarama yapmak** daha kolay ve hızlı
- Global bir sorun olan *A. fumigatus*'ta **azol direnci ülkemiz** için çok sorun değil (**%3,3**)
- **Yeterli doz**: **Azol** alanlarda **TDM**
- Antifungal yönetim **ekip** işidir.


Isınan bir gezegendeyiz...