KLİMİK 2023

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İnvazif Aspergilloz;

Sorunun büyüyen boyutlarının yönetimi nasıl olmalı?

Dr. Süda TEKİN

Koç Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

14 Mart 2023

MİÇG

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].

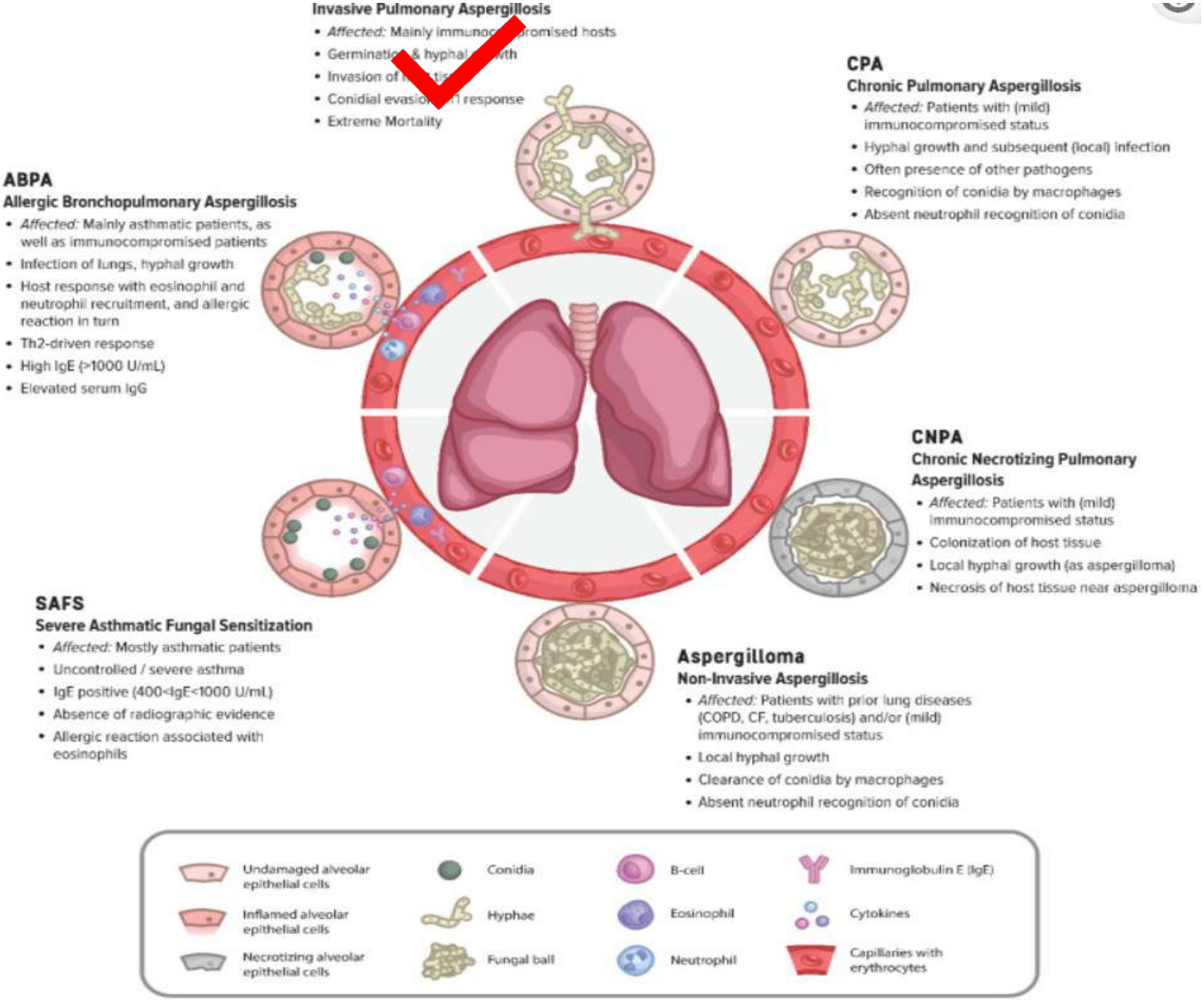
*Fungal causes of eumycetoma include *Madurella mycteomatis*, *Aspergillus spp.*, *Nocardia spp.*, *Fusarium spp.*

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.

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*

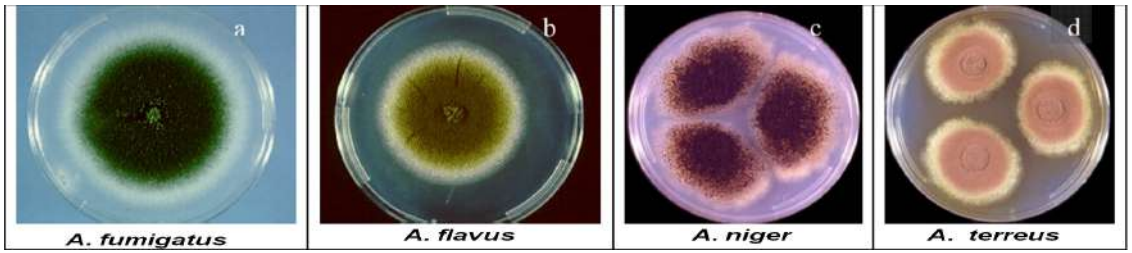


Table 1. Important studies regarding invasive fungal disease in allogenic HSCT recipients.

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

Distribution of invasive fungal infections: Molecular epidemiology, etiology, clinical conditions, diagnosis and risk factors: A 3-year experience with 490 patients under intensive care

Zeinab Borjian Boroujeni [a], Sina Shamsaei [b], Mohammad Yarahmadi [c], Muhammad Ibrahim Getso [d], Alireza Salimi Khorashad [e], Leila Haghighi [b], Vahid Raissi [a,c,**], Mahdi Zareei [a], Anita Saleh Mohammadzade [f], Vahid Moqarabzadeh [g], Ameneh Soleimani [h], Farid Raeisi [i], Moein Mohseni [f], Maedeh Sadat Mohseni [j], Omid Raiesi [k,*]

Çalışmaya **1477 YBÜ** hastası alınmış

Bunlardan **490 İFİ**

✓*Candida* spp. %68.8

✓***Aspergillus* spp. %22**

✓*Zygomycetes* spp. %4.3

Species-specific distribution of the etiology of systemic fungal infections.

Fungus	No. of patients (%)			P-value
	2016 (n = 609)	2017 (n = 456)	2018 (n = 412)	
Actinomyces	3 (0.5)	1 (0.22)	0 (0)	0.089
Alternaria Alternata	1 (0.16)	1 (0.22)	0 (0)	0.7857
Aspergillus Clavatus	2 (0.33)	0 (0)	0 (0)	0.1431
Aspergillus Flavus	20 (3.3)	23 (5.1)	31 (7.52)	**0.0001***
Aspergillus Fumigatus	4 (0.65)	6 (1.3)	8 (1.94)	**0.0001***
Aspergillus Niger	1 (0.16)	3 (0.65)	4 (0.97)	**0.0001***
Aspergillus Terreus	2 (0.32)	3 (0.65)	0 (0)	0.2464
Aspergillus Tubigensis	0 (0)	1 (0.22)	0 (0)	0.1444
Candida Albicans	46 (7.6)	45 (9.8)	17 (4.1)	0.3251
Candida glabrata	18 (2.9)	25 (5.4)	35 (8.5)	**0.0001***
Candida parapsilosis	15 (2.4)	19 (4.2)	19 (4.6)	**0.0001***
Candida tropicalis	9 (1.4)	11 (2.4)	15 (3.6)	**0.0001***
Candida dubliniensis	9 (1.4)	8 (1.7)	5 (1.2)	0.3330
Candida kefyr	5 (0.8)	4 (0.87)	3 (0.72)	0.7420
Candida krusei	3 (0.49)	4 (0.87)	4 (0.97)	**0.0001***
Candida guilliermondii	4 (0.65)	5 (1.1)	2 (0.48)	0.4857
Candida lusitaniae	0 (0)	2 (0.32)	3 (0.72)	**0.0001***
Candida intermedia	2 (0.33)	0 (0)	0 (0)	0.2887
Cryptococcus spp	1 (0.16)	1 (0.22)	1 (0.24)	0.0677
Fusarium spp	0 (0)	1 (0.22)	3 (0.72)	**0.0001***

Microbial Pathogenesis. **2021**; 152: 104616.

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],

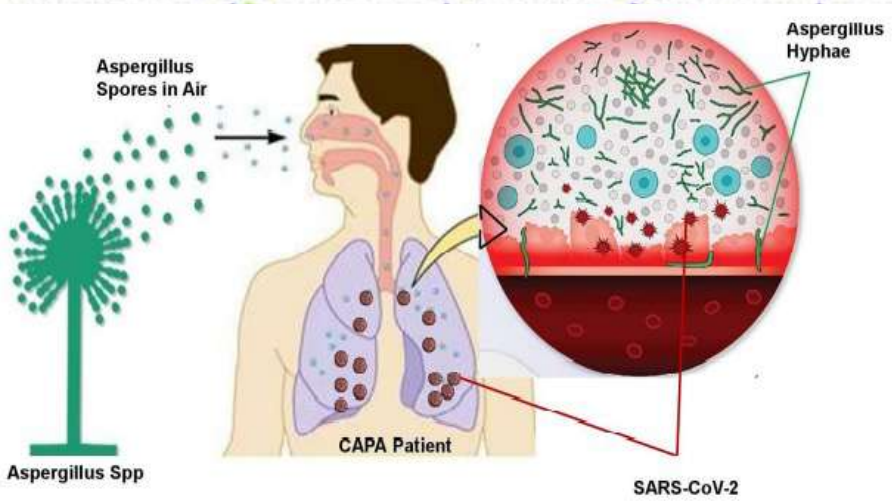
YBÜ'de İFİ

- **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)

Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study



lo Maccaro,[1] Linda Bussini,[1] Giacomo Fornaro,[1] Tommaso Tonetti,[3]
ssandra Moroni,[2] Simone Ambretti,[2] Filippo Trapani,[1] Oana Vatamanu,[1]
ddalena Giannella,[1] and Pierluigi Viale[1]; for the PREDICO Study Group[a]

ogna, Italy, [2]Operative Unit of Microbiology, University of Bologna, Policlinico Sant'Orsola,
rsola, Bologna, Italy, [4]Intensive Care Unit, Maggiore Hospital, Bologna, Italy, and [5]Cardio-

y aspergillosis among intubated patients with critical COVID-19

ı microbiologically confirmed COVID-19 receiving mechanical
ocol for invasive pulmonary aspergillosis with bronchoalveolar
ays and in case of clinical deterioration. Cases were classified as coronavirus-associated pulmonary aspergillosis (CAPA) according to previous consensus definitions. The new definition was compared with putative invasive pulmonary aspergillosis (PIPA).

Results. 108 patients were enrolled. Probable CAPA was diagnosed in 30 (27.7%) patients after a median of 4 (2–8) days from intensive care unit (ICU) admission. Kaplan-Meier curves showed a significantly higher 30-day mortality rate from ICU admission among patients with either CAPA (44% vs 19%, $P = .002$) or PIPA (74% vs 26%, $P < .001$) when compared with patients not fulfilling criteria for aspergillosis. The association between CAPA (OR, 3.53; 95% CI, 1.29–9.67; $P = .014$) or PIPA (OR, 11.60; 95% CI, 3.24–41.29; $P < .001$) with 30-day mortality from ICU admission was confirmed, even after adjustment for confounders with a logistic regression model. Among patients with CAPA receiving voriconazole treatment (13 patients; 43%) a trend toward lower

Conclusions. We found a high incidence of CAPA among critically ill COVID-19 patients and its occurrence seems to change the natural course of disease.

Keywords. SARS-CoV-2; COVID-19; severe respiratory failure; aspergillosis; voriconazole.

IDSA Infectious Diseases Society of America · hivma hivmedicine association · OXFORD

Clinical Infectious Diseases

MAJOR ARTICLE

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]

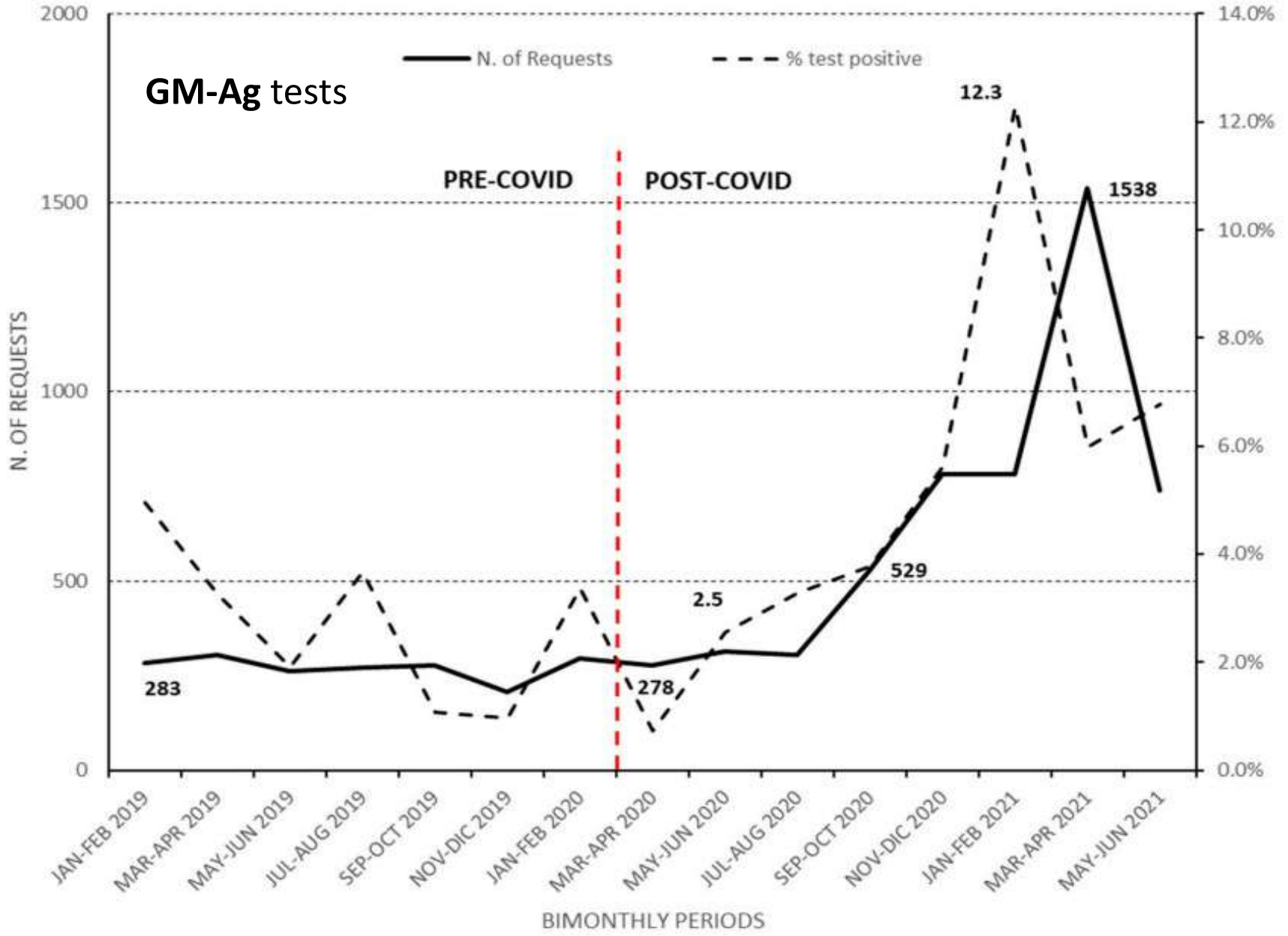
COVID-19 hastalarında ***Aspergillus*** **ko-**infeksiyonlarını (**CAPA**)

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

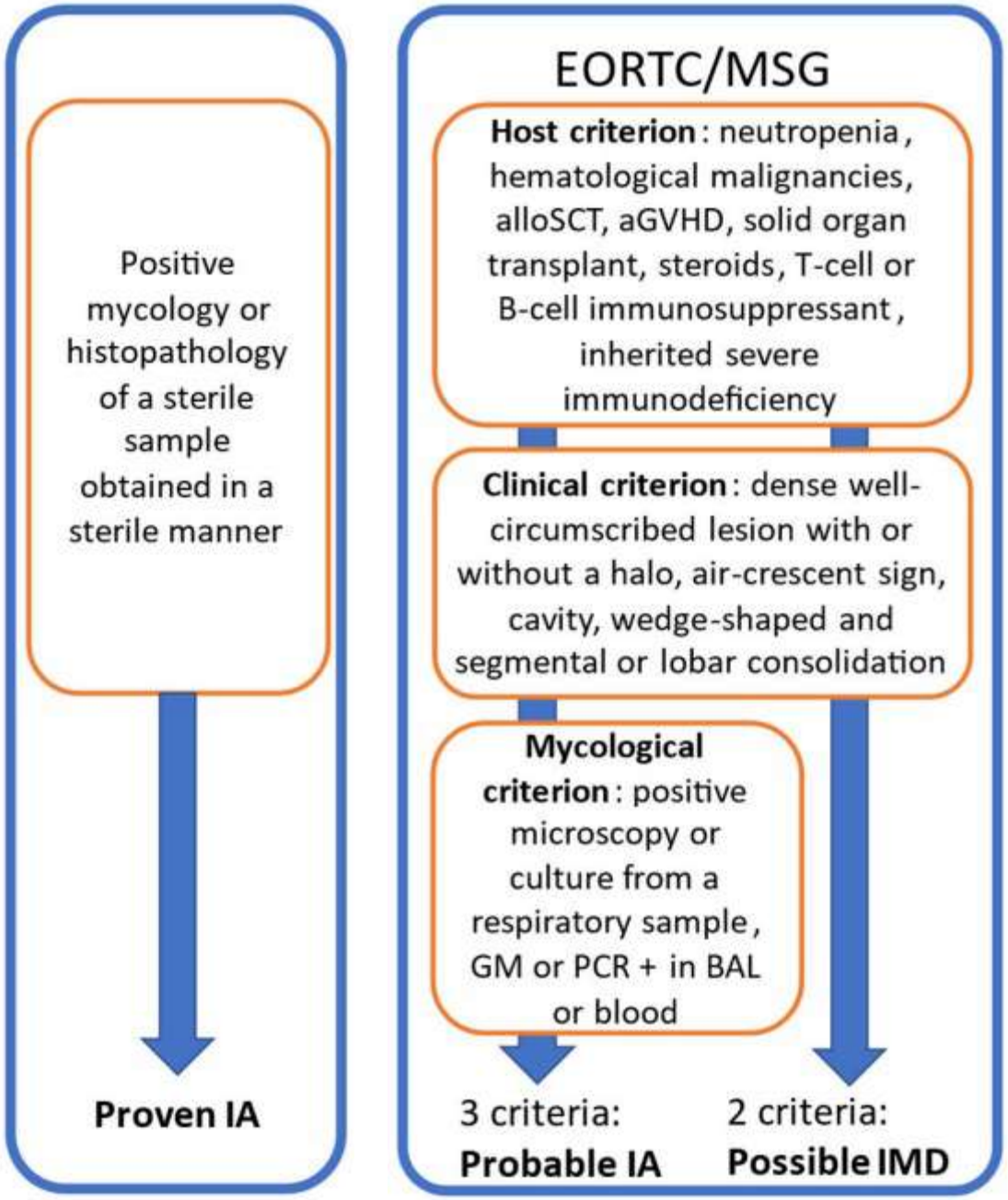
Clinical Infectious Diseases

SUPPLEMENT ARTICLE

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

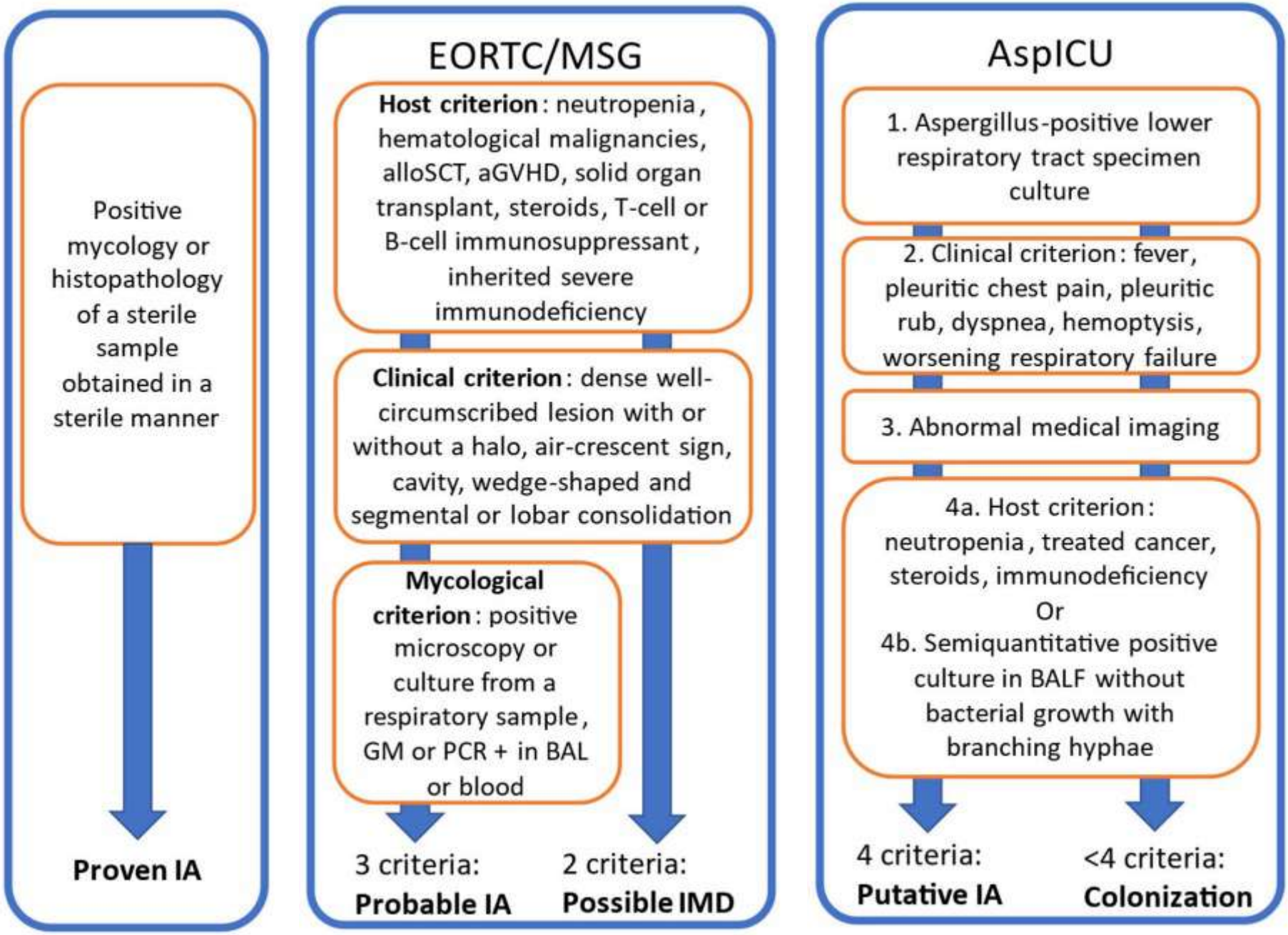
Matteo Bassetti,[1,2] Elie Azoulay,[3,4] Bart-Jan Kullberg,[5] Markus Ruhnke,[6] Shmuel Shoham,[7] Jose Vazquez,[8] Daniele Roberto Giacobbe,[1] and Thierry Calandra[9]

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: • Histo/cytopathologic or direct microscopic examination (hyphae + tissue damage) • Positive culture from tissue
	Probable IPA	**Host factors**: Neutropenia, malignant hemopathy, transplant, prolonged corticosteroids (>0.3mg/kg >3weeks/2months), immunosuppressive drugs…	**CT pattern**, at least 1: • Dense, well-circumscribed lesion (±halo) • Air crescent sign • Cavity • Consolidation	At least 1: • Positive direct microscopy or culture of a respiratory sample (sputum, tracheal aspirate, BAL) • BAL GM ≥1 • Serum GM ≥1 • BAL GM ≥0.8 and serum GM ≥0.7 • 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: Fever despite antibiotics >3d or recrudescent after 48h defervescence, dyspnea, hemoptysis, chest pain, pleuritic rub, worsening respiratory insufficiency	**Chest X-ray or CT scan:** Abnormal imaging (any infiltrate)	**In the absence of host risk factor:** Positive direct microscopy (hyphae) and culture of BAL
		± Host risk factors: 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 Pathologic changes of the tissue Morphology of the *Aspergillus*	Invasive operation High requirements for specimen quality Technology dependent on the technician Time-consuming False-negative
Fungal biomarker assay	Early detection Non-invasive Various sample resources Platform widely available Rapid turnaround time	False-positive False-negative Unknown pathogen species Unknown infection site
Aspergillus polymerase chain reaction (PCR) test	Specific species Various sample resources Rapid turnaround time	Lack of standardization Contamination can be problematic
CT scanning	Fast and non-invasive Location of infection site Lesion size and number	Non-specific Pathogen not identified 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.

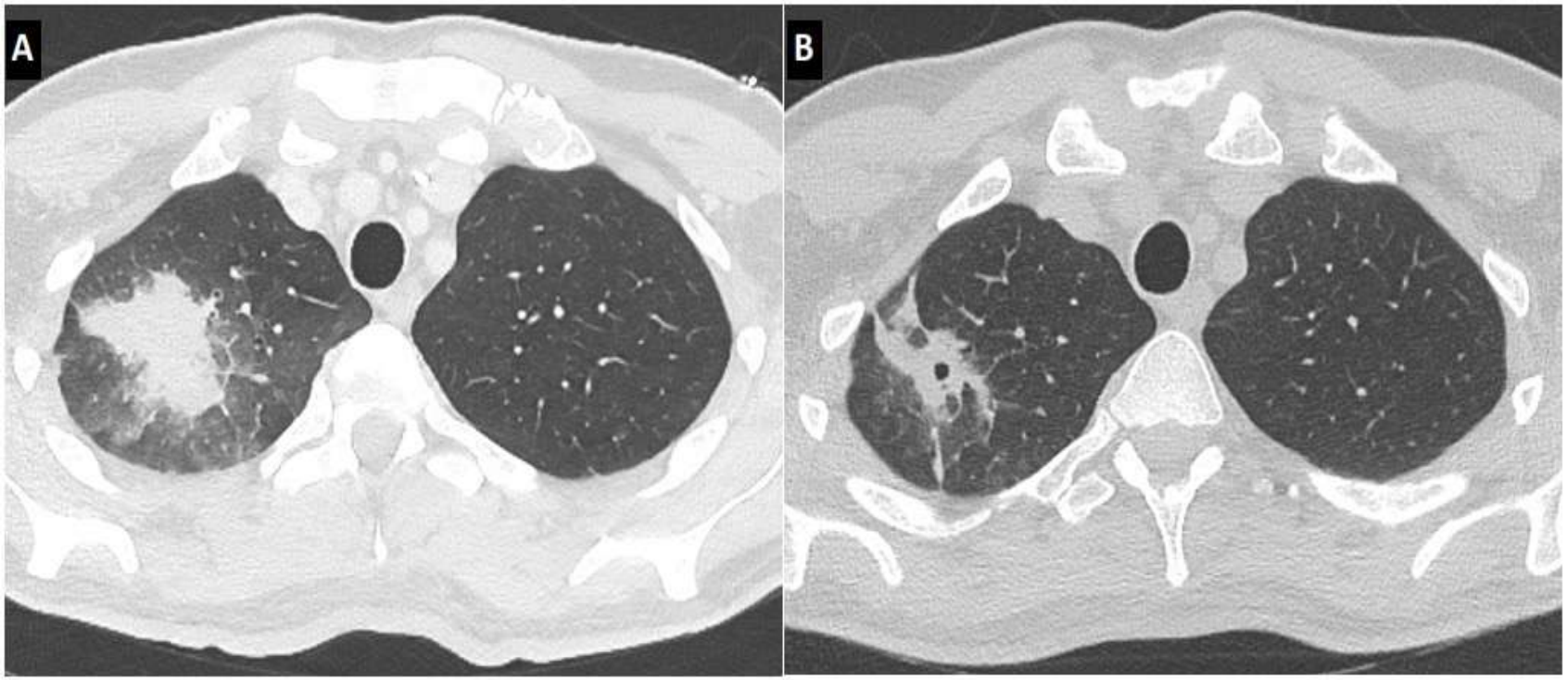
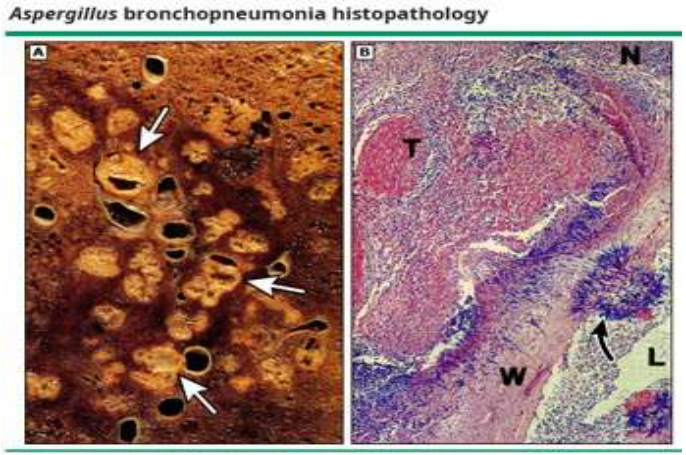


Figure 1. Invasive aspergillosis in a refractory acute myeloblastic leukemia patient. (**A**) CT-scan at diagnosis, showing a nodule surrounded by a halo. (**B**) CT-scan 4 weeks later, showing a small cavity.



J Fungi. 2023; 9: 131

International Journal of
Molecular Sciences

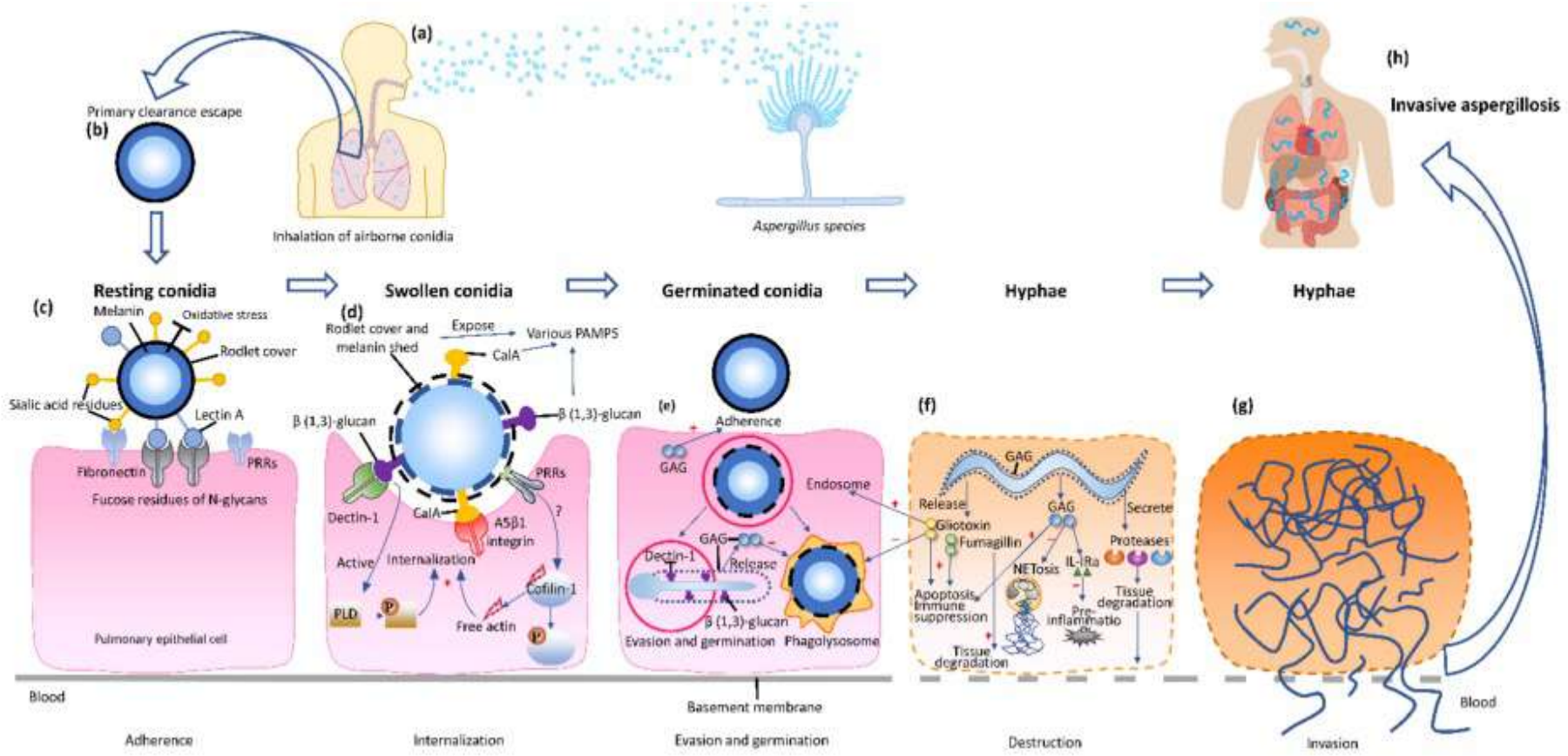
Int J Mol Sci. **2022**; 23: 5563.

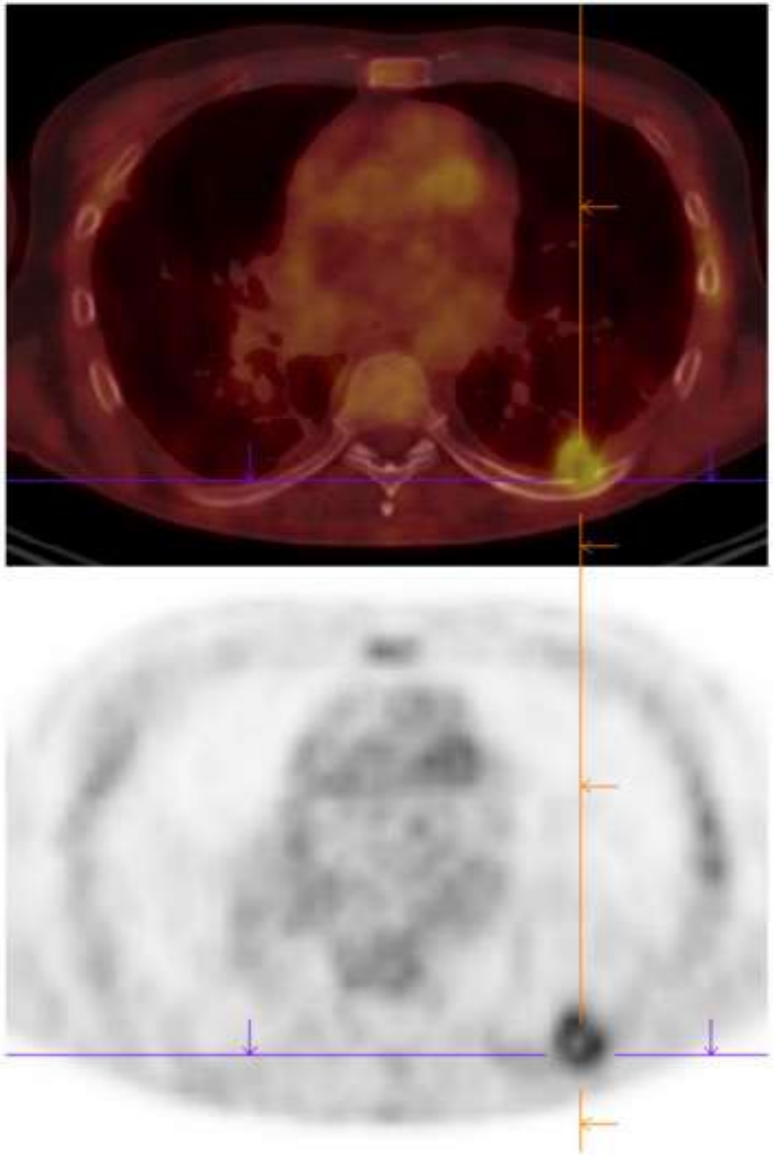
MDPI

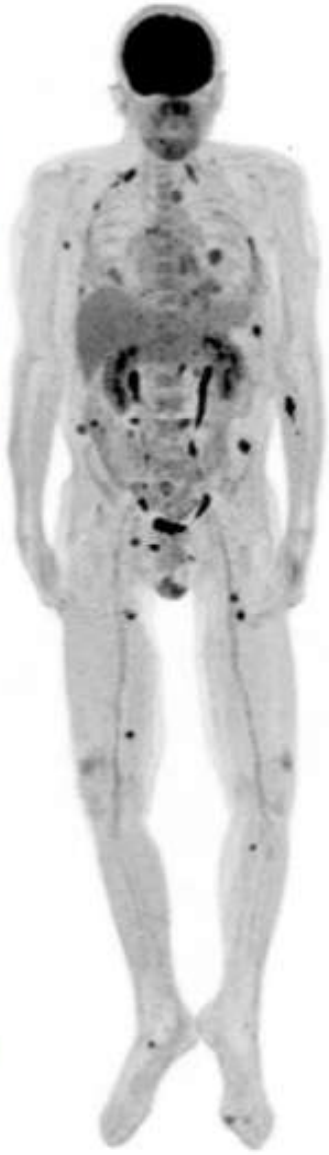
Review

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?**

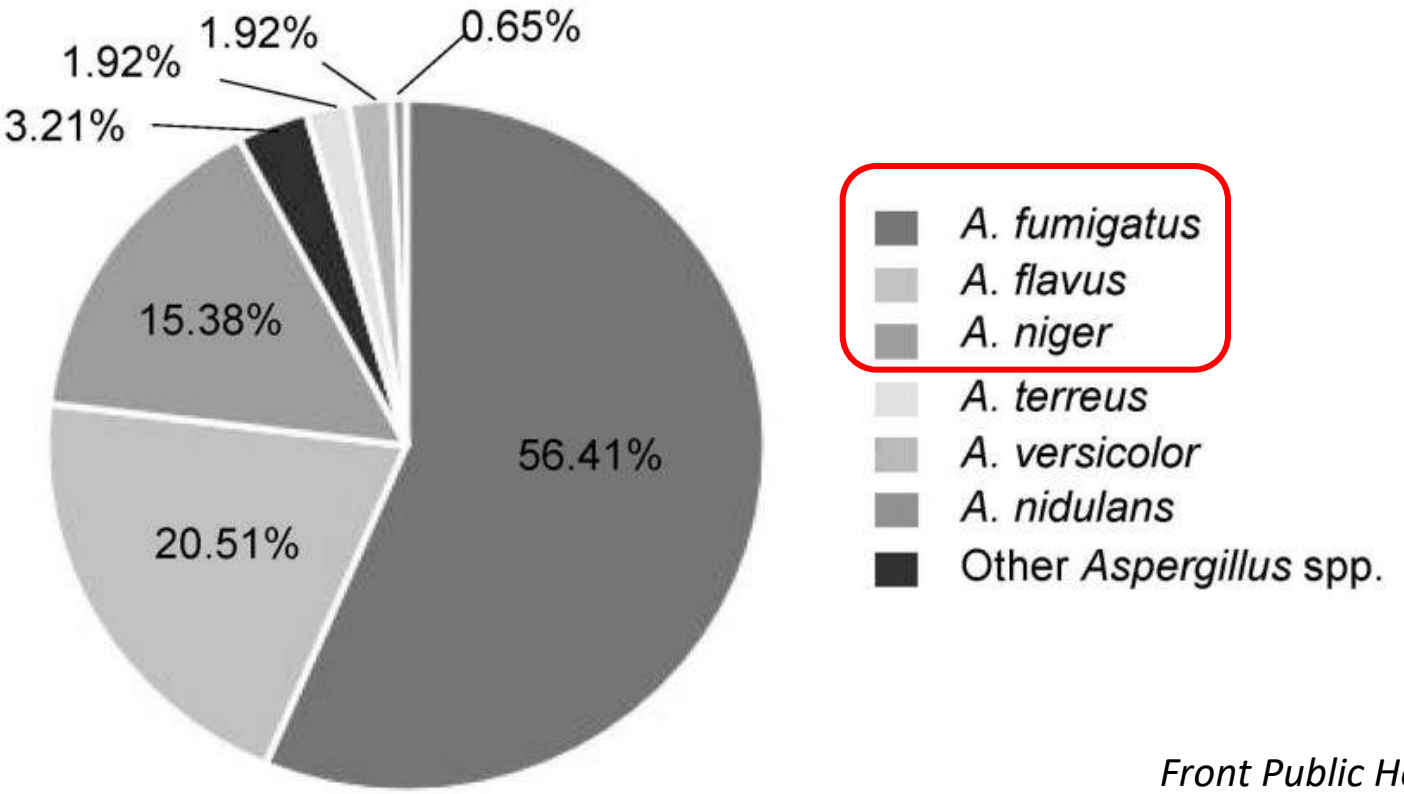
4. Azol direnci sorun mu?

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

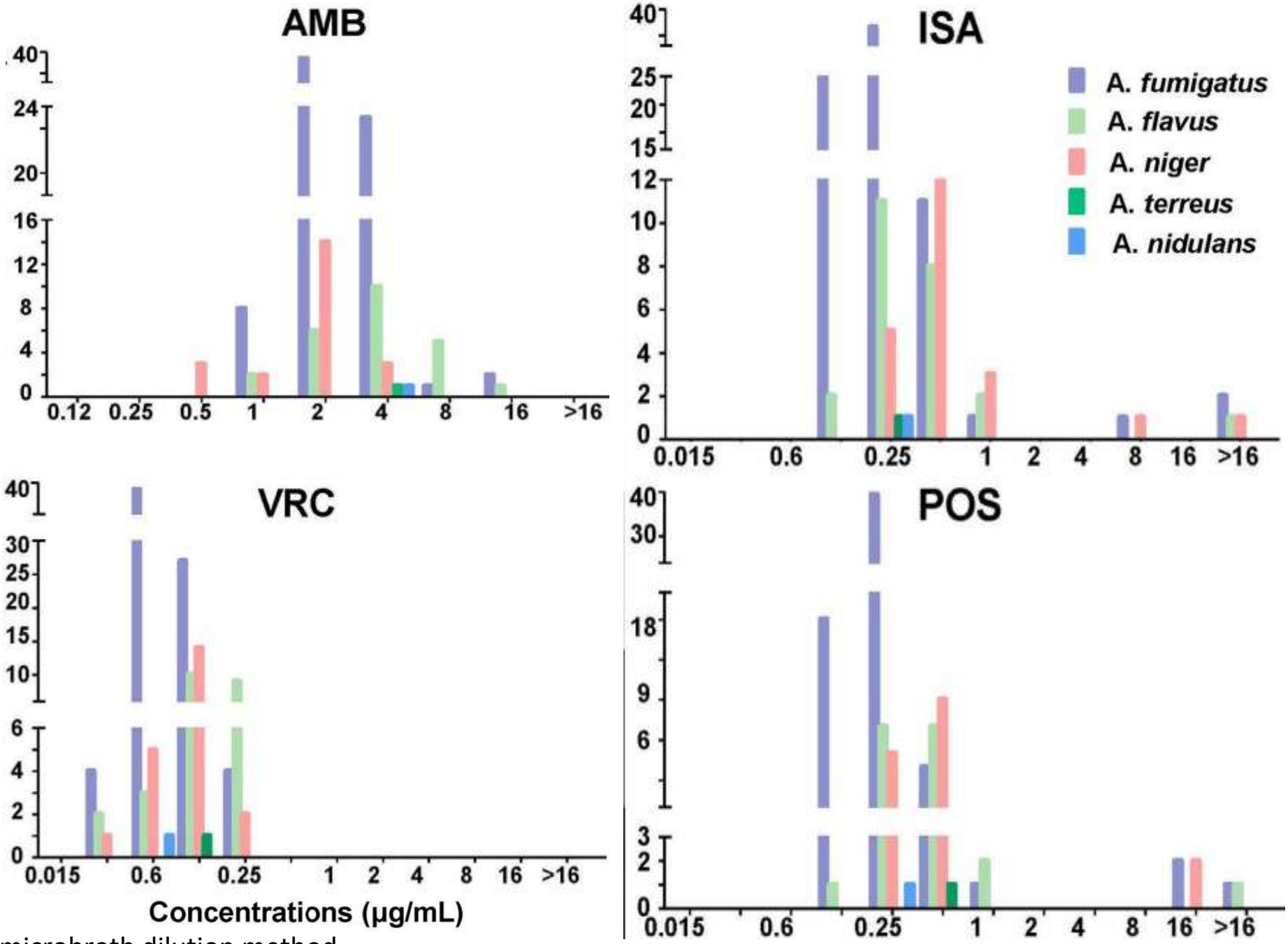
Frontiers in Public Health

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

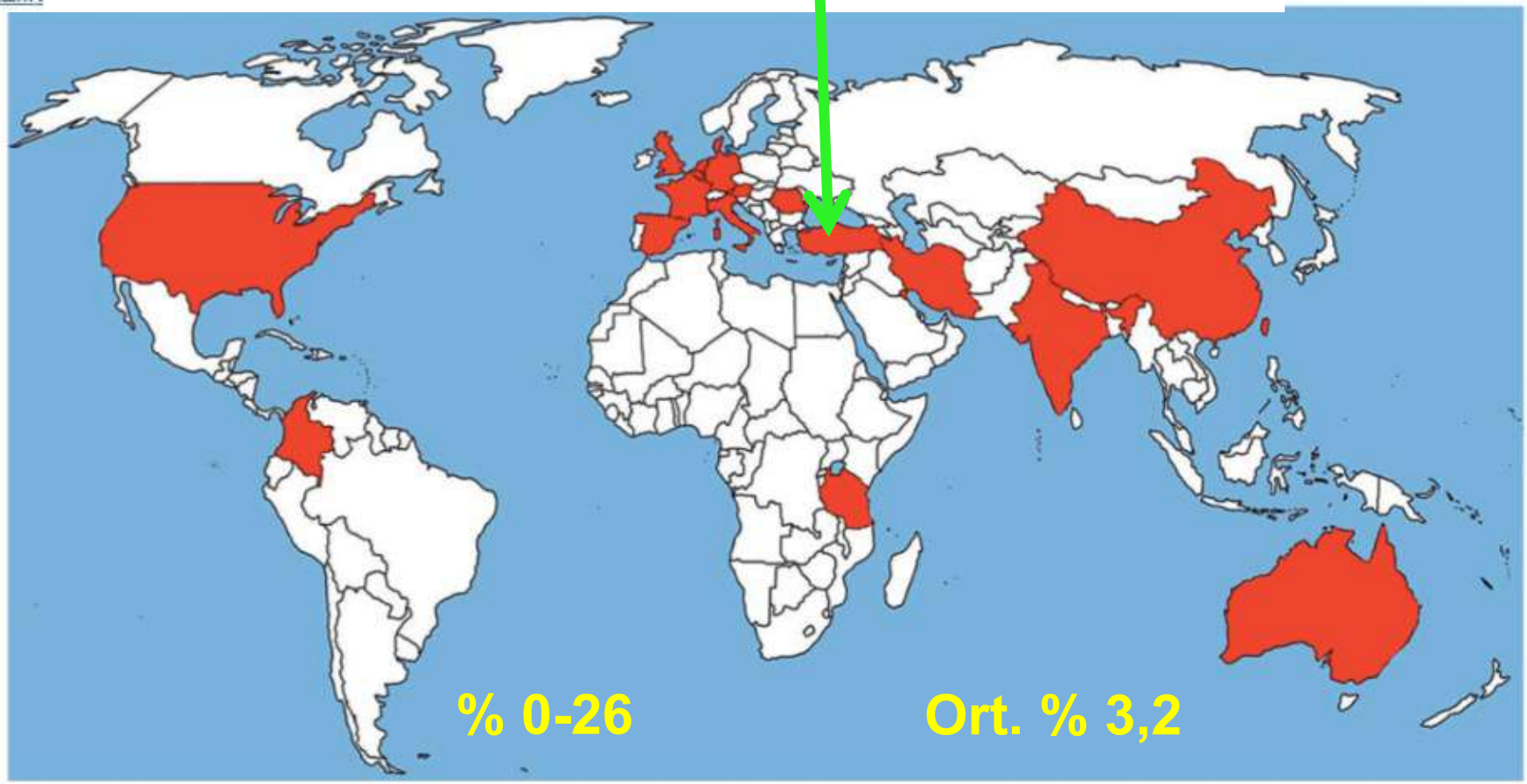


Figure 1. Shaded areas show countries that have reported the TR_{34}/L98H and TR_{46}/Y121F/T289A resistance mechanism in clinical or environmental *Aspergillus fumigatus* isolates.

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

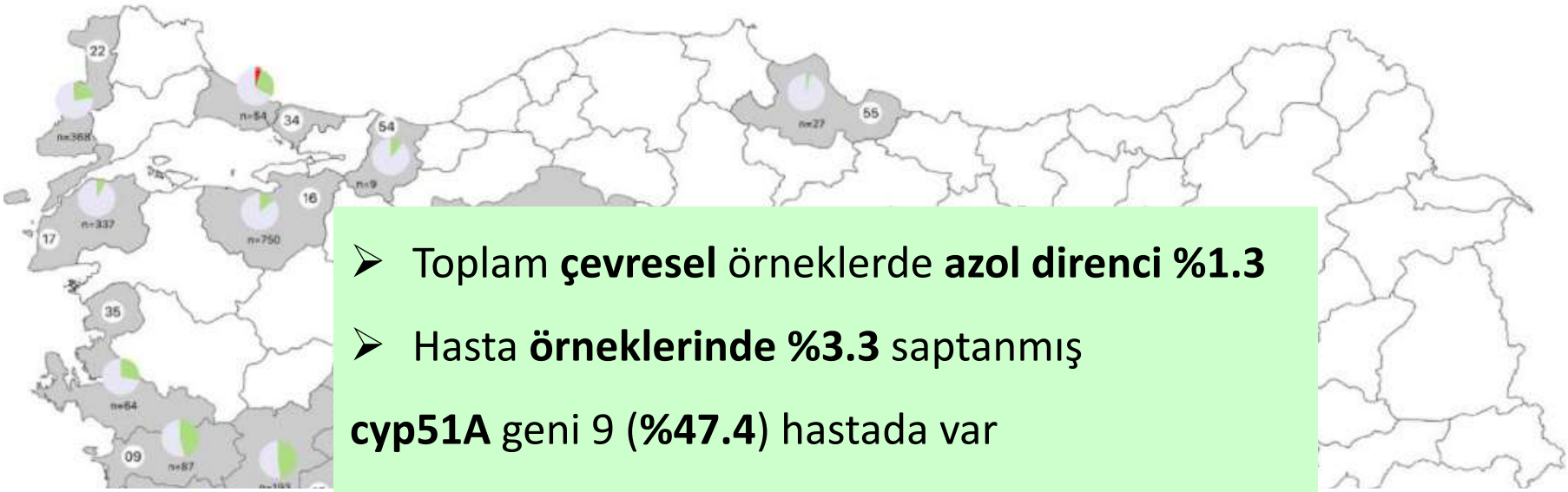
Beyza Ener[1]*, Çağrı Ergin[2], Dolunay Gülmez[3], Harun Ağca[1], Melek Tikveşli[4], Seçil Ak Aksoy[5], Müşerref Otkun[6], Ali Korhan Sığ[3], Dilara Öğünç[7], Betil Özhak[7], Tuncay Topaç[8], Aslı Özdemir[6], Dilek Yeşim Metin[9], Süleyha Hilmioğlu Polat[9], Yasemin Öz[10], Nedret Koç[11], Mustafa Altay 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.

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

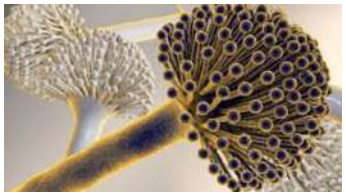
İnvazif Fungal İnfeksiyon Yönetimi

I. 2016 IDSA

II. 2017 ECIL-6

III. ESCMID (Küfler 2018)

IV. Yeni çalışmalar



Lancet Infect Dis 2020

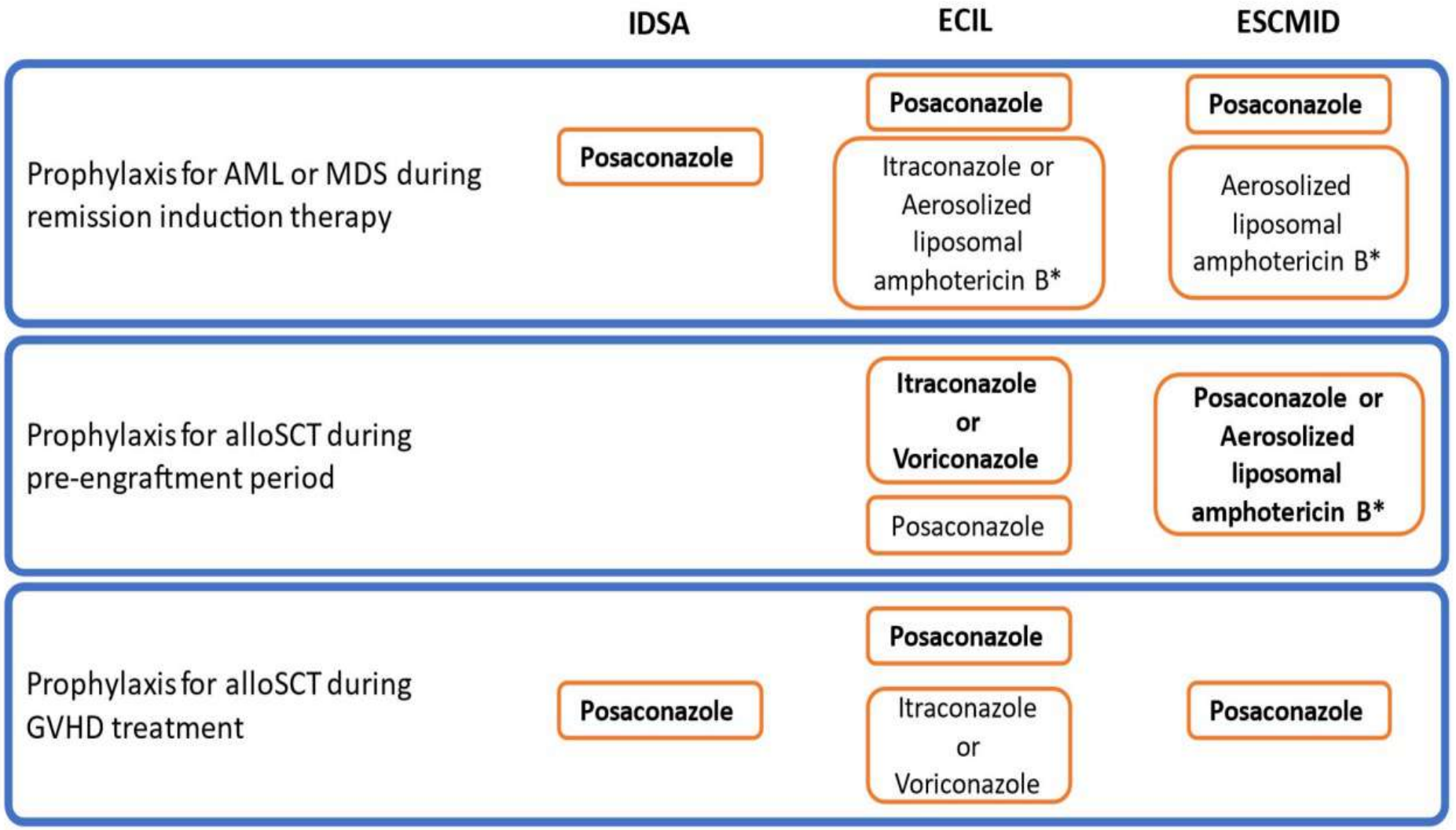
Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance

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

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

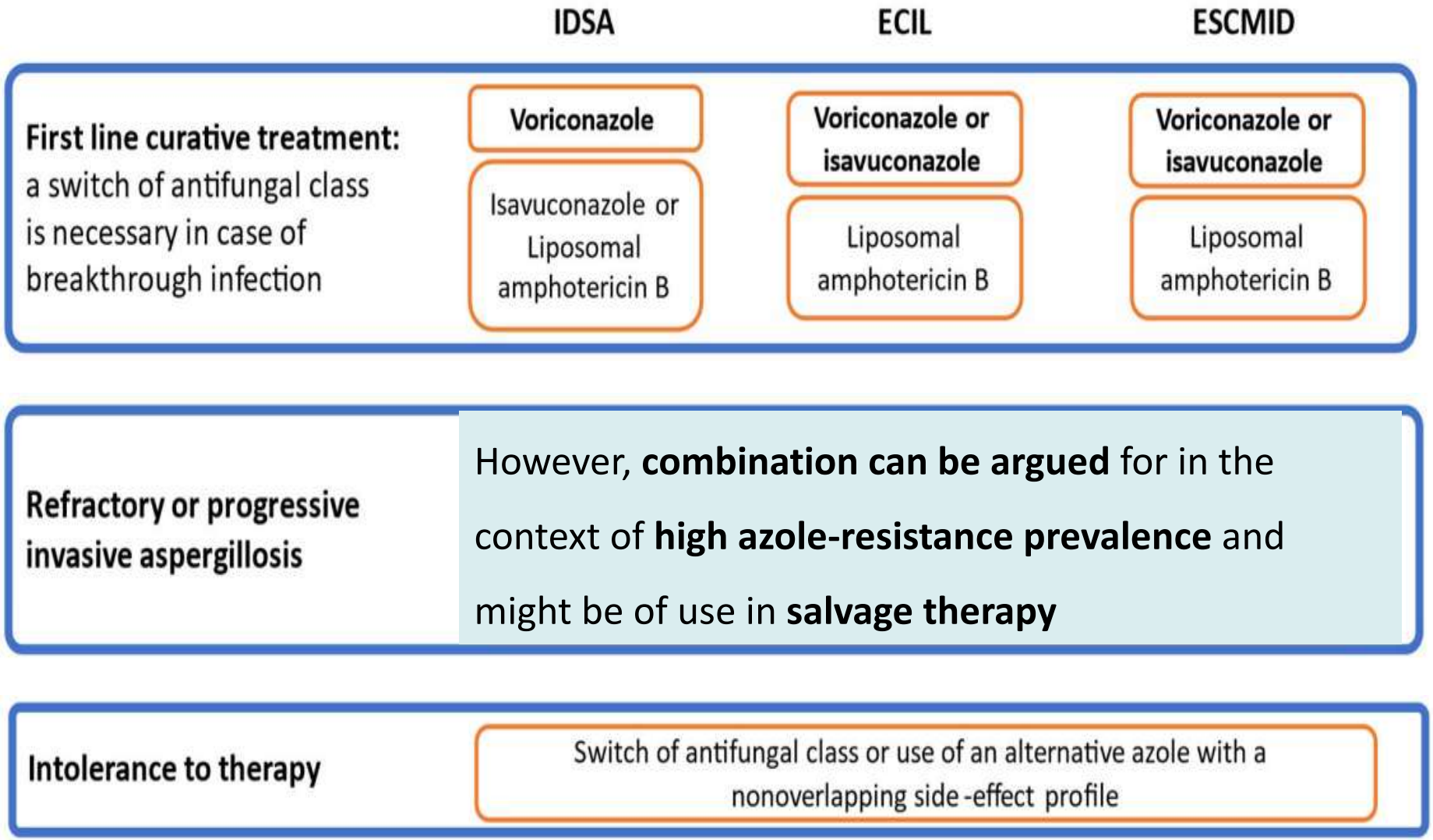
Popülasyon	Tedavi seçeneği	ÖG/KK
1. Nötropeni (non-allo HSCT alıcıları) 2. Allo-HSCT (nötropeni) 3. Allo-HSCT (w/o nötropeni) veya diğer nötropenik olmayanlar	**İsavukonazo**l 200 mg IV tid gün 1 ve 2, sonra 200 mg qd oral	AI
	Vorikonazol 2x6 mg/kg IV (oral 400 mg bid) ilk gün, 2x4 mg/kg IV (oral 200-300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

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



IDSA. *J Fungi Basel*. 2019
ECIL. *J Antimicrob Chemother*. 2018
ESCMID. *Clin Microbiol Infect*. 2018

J Fungi. 2023; 9: 131



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 Oral: 4 mg/kg twice daily	A	I	• Caution if already on triazole prophylaxis • 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 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 • 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

*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**

- ✓ **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

MİÇG
KLİMİK DERNEĞİ MANTAR
İNFEKSİYONLARI ÇALIŞMA GRUBU

Soru(n) 5

‘Breakthrough’ IA nedir ve nasıl

yönetilmelidir?

Clinical Infectious Diseases

INVITED ARTICLE

IMMUNOCOMPROMISED HOSTS: David Snydman, Section Editor

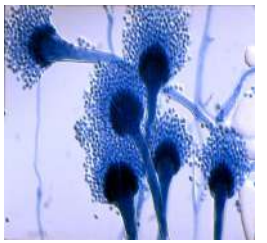
CID. 2018; 67(10):1621–30

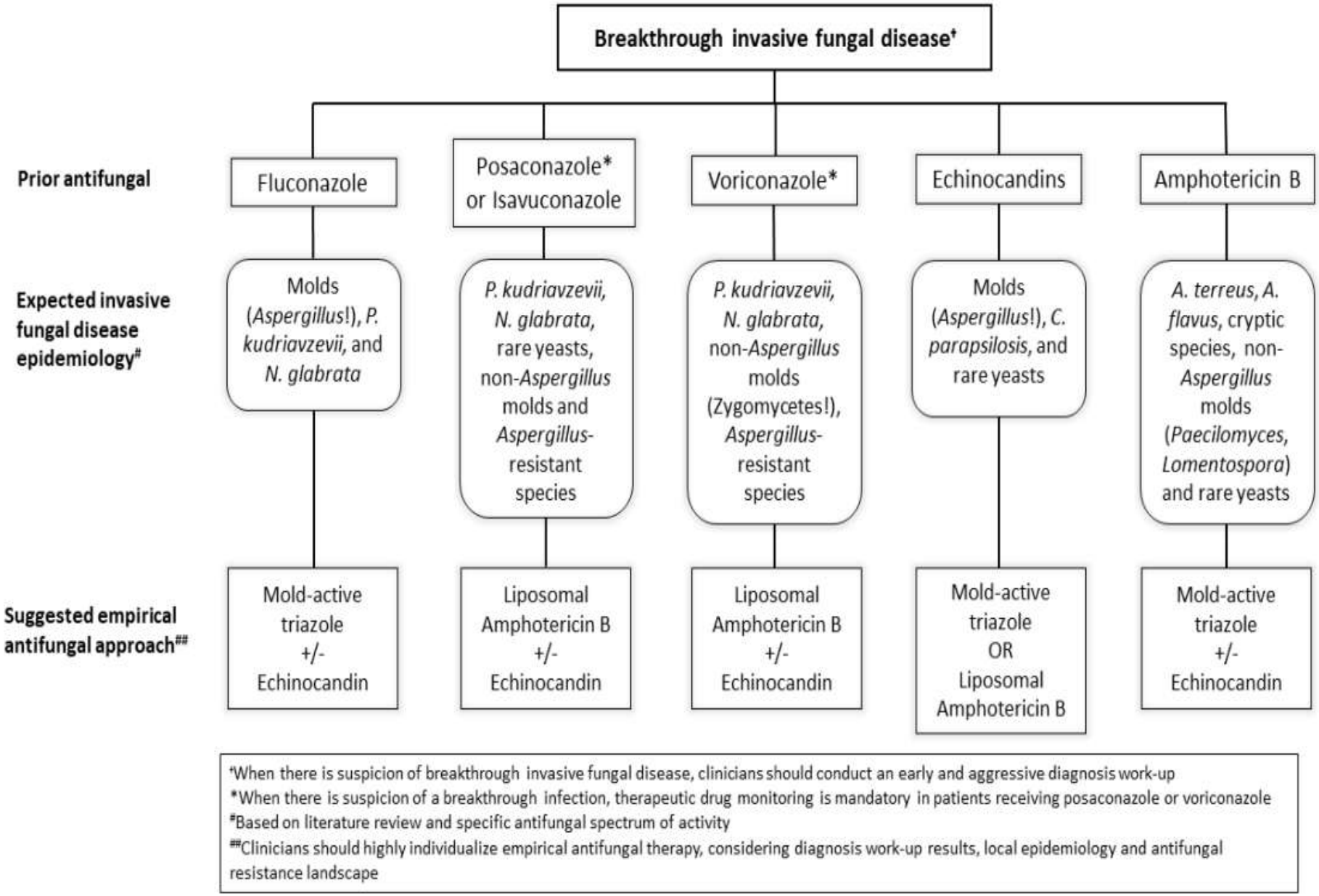
Breakthrough Invasive Mold Infections in the Hematology Patient: Current Concepts and Future Directions

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

- Hematolojik maligniteli hastalarda triazol profilaksisine rağmen İFİ görülme sıklığı artmakta
- «**Breakthrough**» İFİ görülmekte (bİFİ)
- **bİFİ**→ Tedavi net değil
- **Yönetimde**; konak, lokal veriler, antifungal direnç

sonuçları ve verilen **profilaksi** durumuna göre karar verilmeli





†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.

Klinik çalışma aşamasındaki antifungaller

Compound	Mode of action	*In vitro* MIC *Aspergillus fumigatus*	*In vivo* activity in murine IA models	Human trials in *Aspergillus*
Agents in clinical trials				
SCY-078 (Ibrexafungerp; Synexis Inc., Jersey City, NJ, USA)	Novel glucan synthase inhibitor	MEC range 0.03–1 μg/mL compared with MEC_{90} of 8 μg/mL and 2 μg/mL for AMB and VRC	*In vivo* murine and pig models	Phase 3 combination therapy with VRC; also ODD
APX001 (Fosmanogepix)[†]	GPI-anchor inhibitor	0.03–0.13 μg/mL	25 mg/kg oral	Phase 2 ongoing
F901318 (Olorofim)	DHODH and pyrimidine biosynthesis inhibitor	<0.06 μg/mL	10 mg/kg oral	Phase 2b ongoing
T-2307[‡]	Affects mitochondrial function	0.01–1.0 μg/mL	Active 1 mg/kg subcutaneous	Phase I

CD101 (**Rezafungin**; Cidara Therapeutics, San Diego, CA, USA)

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

MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

Maruziyetten Korunma

- Hastalar hastanede **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).

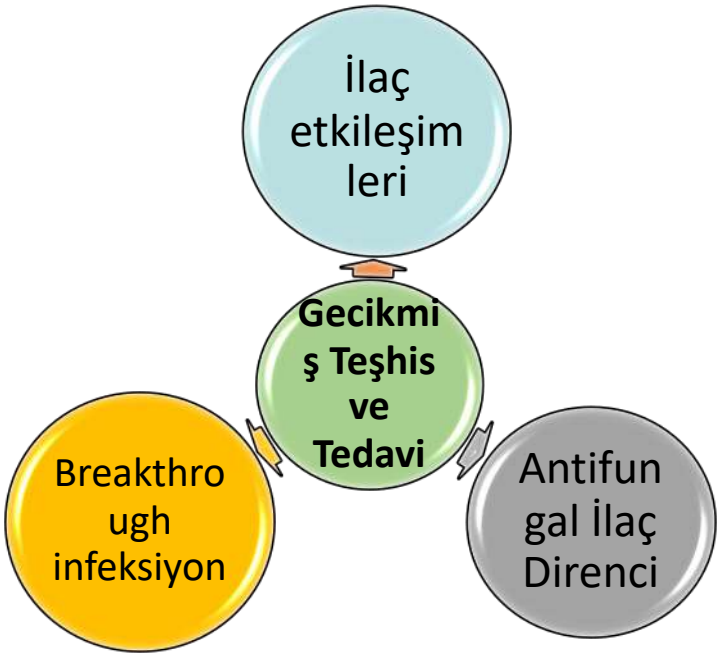
Ullmann AJ, et al. ESCMID Guide. *CMI*. 2018. e1ee38

REVIEW

Challenges and research priorities to progress the impact of antimicrobial stewardship

Matteo Bassetti MD, PhD[1,2,3], Daniele Roberto Giacobbe MD[2,3], Antonio Vena MD, PhD[1], Adrian Brink MMed[4]

[1]Infectious Diseases Clinic, Department of Medicine, University of Udine, Italy; [2]Infectious Diseases Unit, Ospedale Policlinico San Martino – IRCCS per l'Oncologia, University of Genoa, Largo R. Benzi, 10, 16132, Genoa, Italy; [3]Department of Health Sciences, DISSAL, University of Genoa, Genoa, Italy; [4]Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa



Özetle;

- İFİ'ler immünokompromize konakta **hayatı tehdit eder**
- Tanısı zor, ancak daha iyi **görüntüleme** ve **yeni biyobelirteç** sayesinde tanı hızlanmakta
- Antifungal **profilaksiyi sınırlanmalı**
- **Lokal veriler**, **direnç sonuçlarının** güncel takip edilmesi gerekli ve önemlidir
- **Yeterli doz**: **Azol** alanlarda **TDM**
- Antifungal yönetim **ekip** işidir.

Rayens E. *Clin Infect Dis*. 2021: 20: ciab336.

Mutluluğun resmi...

Yaşasın Cumhuriyet