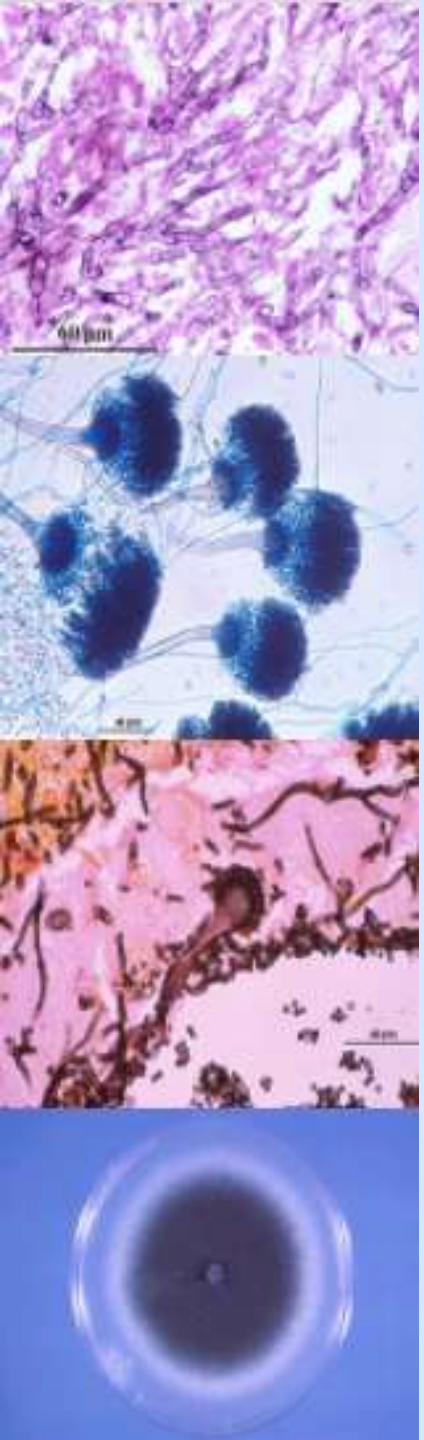


MİÇG
KLİMİK DERNEĞİ MANTAR İNFEKSİYONLARI ÇALIŞMA GRUBU

İnvazif Aspergilloz İnfeksiyonlarının Yönetiminde Güncel Yaklaşımlar

Dr. Funda MEMİŞOĞLU
İnönü Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

Fig. 1. WHO fungal priority pathogens list (WHO FPPL)

- Mantar enfeksiyonlarında küresel artış
  - COVID-19 salgını
  - İklim değişikliği
  - İnsan ve hayvan yerleşiminde değişiklikler
  - Antifungal ilaçlara karşı artan direnç
  - Bağışıklığı baskılanmış hasta sayısında artış

WHO releases first-ever list of health-threatening fungi. 25 October 2022.

Journal of *Fungi*

Review

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

Pedro Puerta-Alcalde * and Carolina Garcia-Vidal

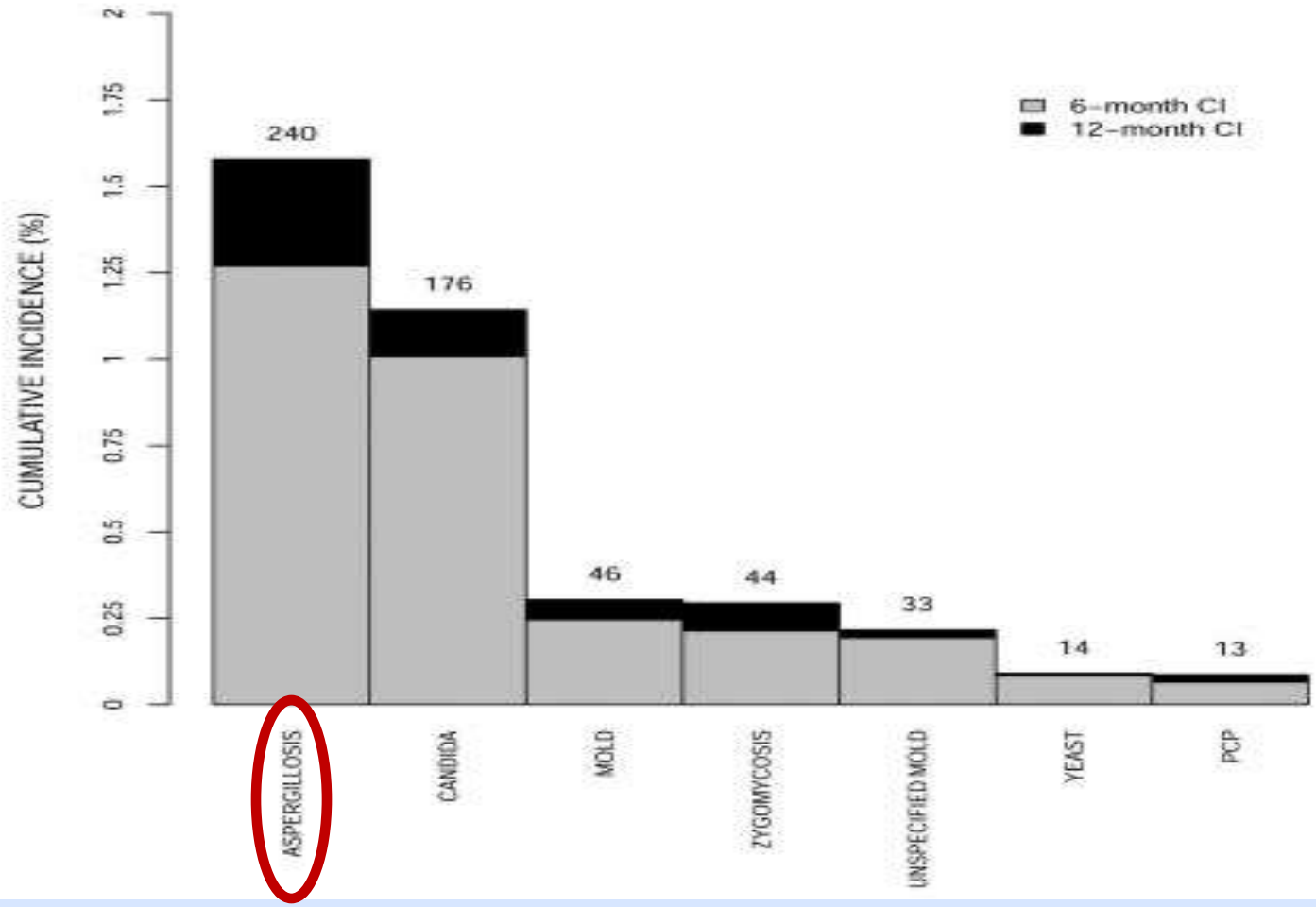
- Kandidemi oranları azalmakta
- En çok izole edilen mantar *Aspergillus fumigatus*
- *Aspergillus niger*
- *Aspergillus terreus*
- *Aspergillus flavus*

J. Fungi **2021**,7,848.

Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database

Clinical Infectious Diseases 2010; 50:1091–1100

Dimitrios P. Kontoyiannis, Kieren A. Marr, Benjamin J. Park, Barbara D. Alexander, Elias J. Anaissie,



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 [1], Sina Shamsaei [2], Mohammad Yarahmadi [3],

Table 4. 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

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

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

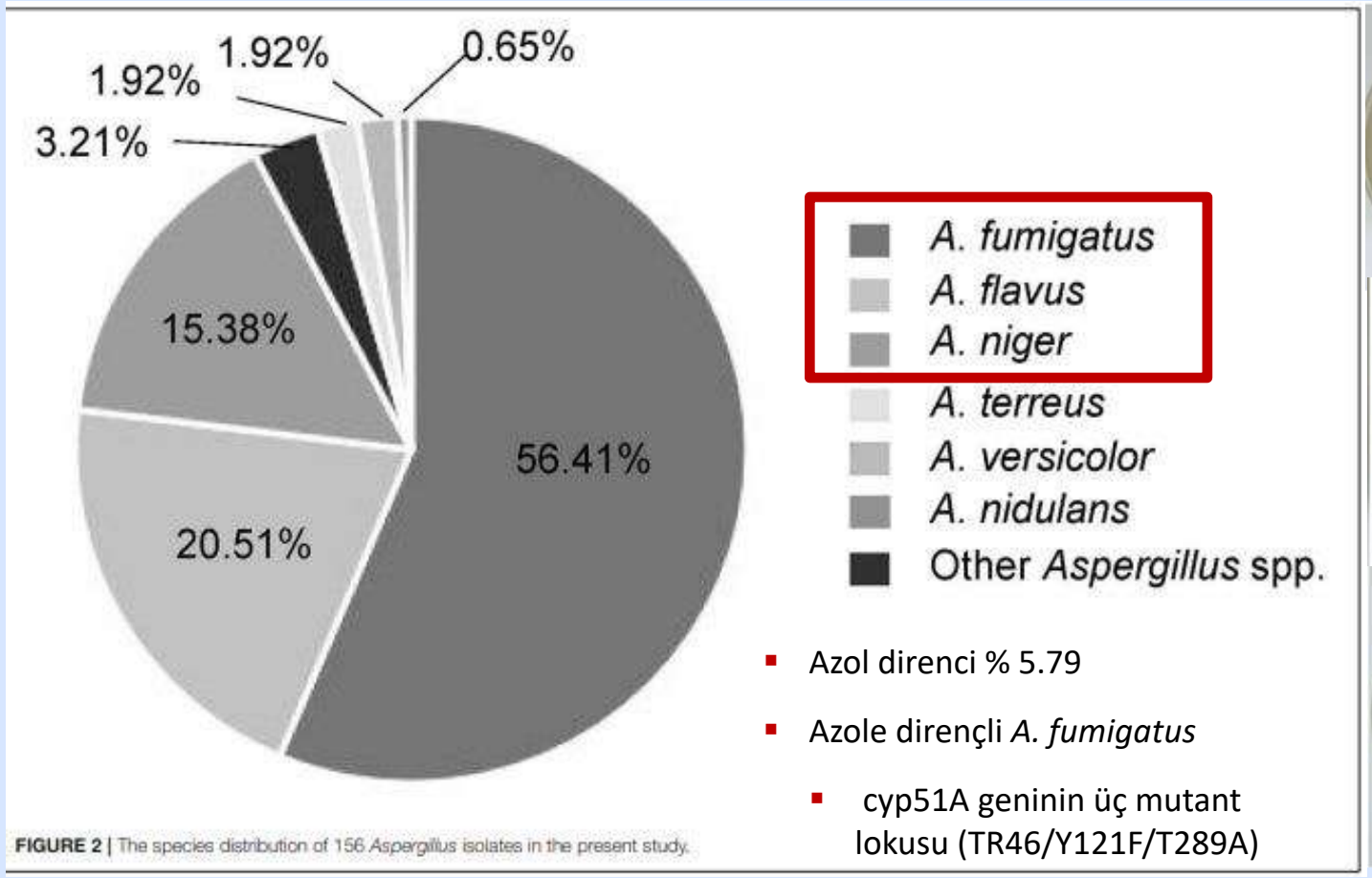
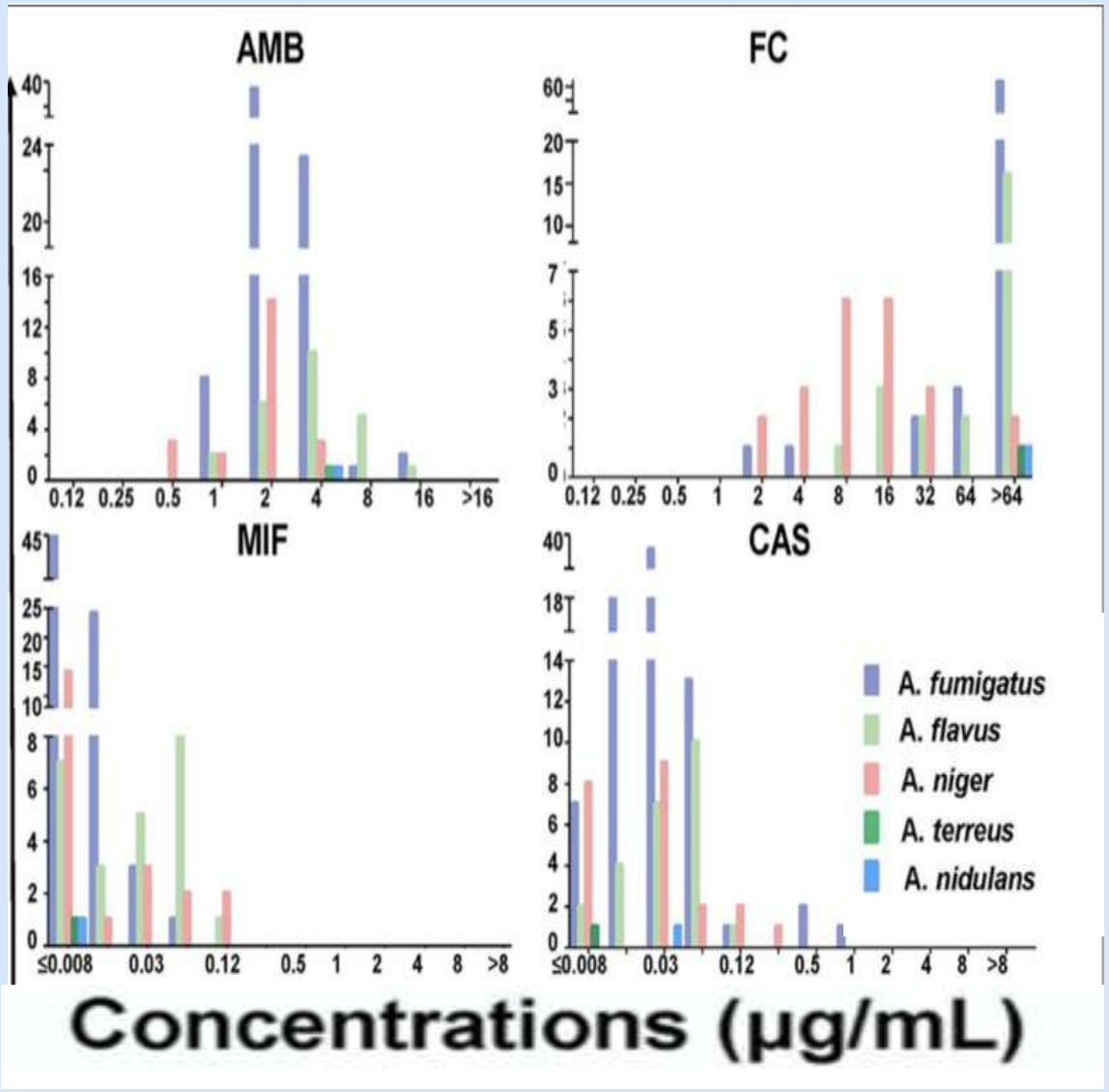


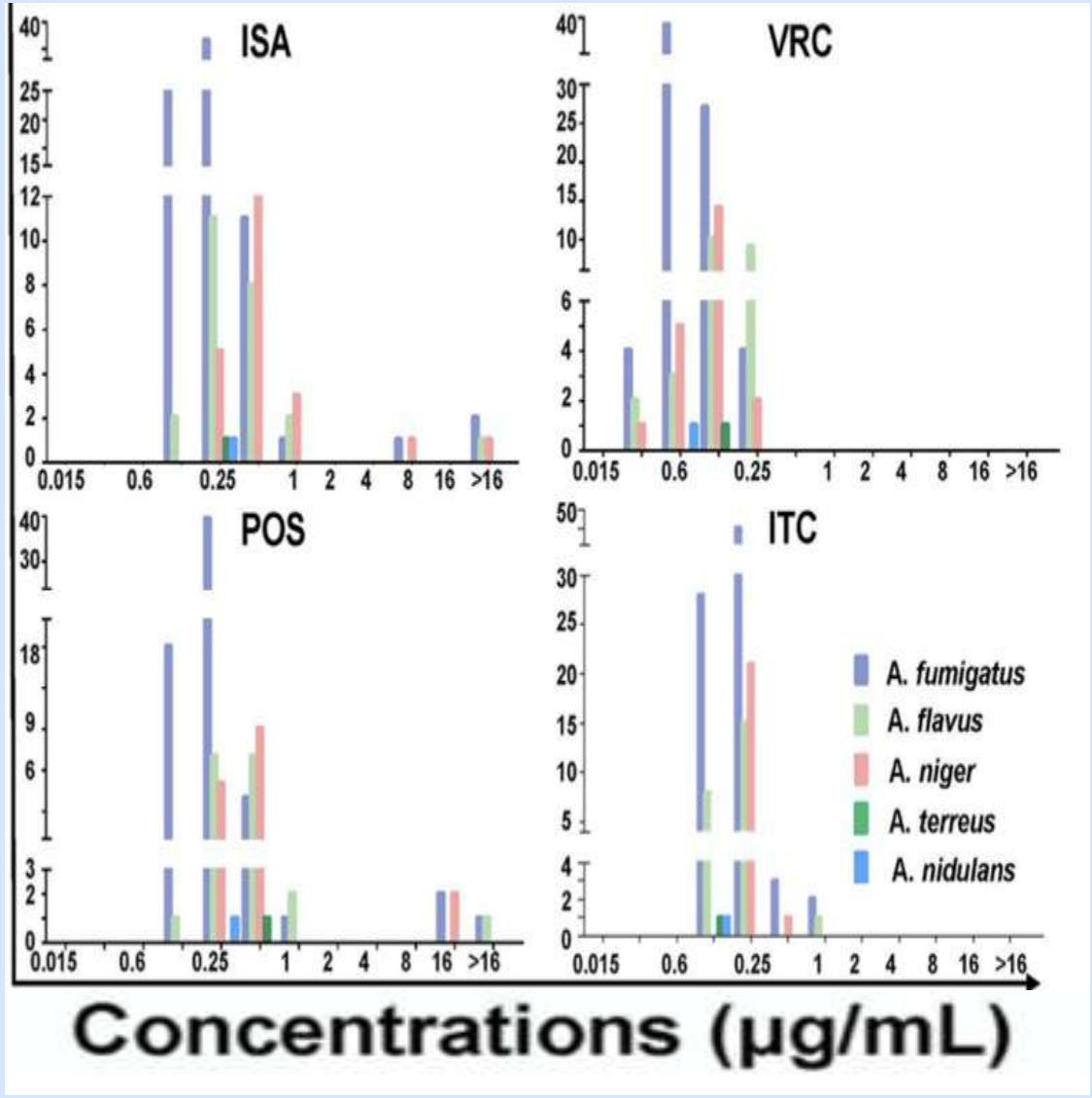
FIGURE 2 | The species distribution of 156 *Aspergillus* isolates in the present study.

- Azol direnci % 5.79
- Azole dirençli *A. fumigatus*
  - cyp51A geninin üç mutant lokusu (TR46/Y121F/T289A)

Front. Public Health 10:835092

Aspergillus spp. MIC dağılımı





ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2018, 56, S83–S92
doi: 10.1093/mmy/myx144
Review Article

Review Article

Triazole resistance surveillance in *Aspergillus fumigatus*

Agustin Resendiz Sharpe[1,*], Katrien Lagrou[1], Jacques F. Meis[2,3],

Figure 1. Countries that have reported triazole resistance in *A. fumigatus*. Countries with triazole resistance are depicted in red, while those with unknown resistance epidemiology are indicated in white.

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],

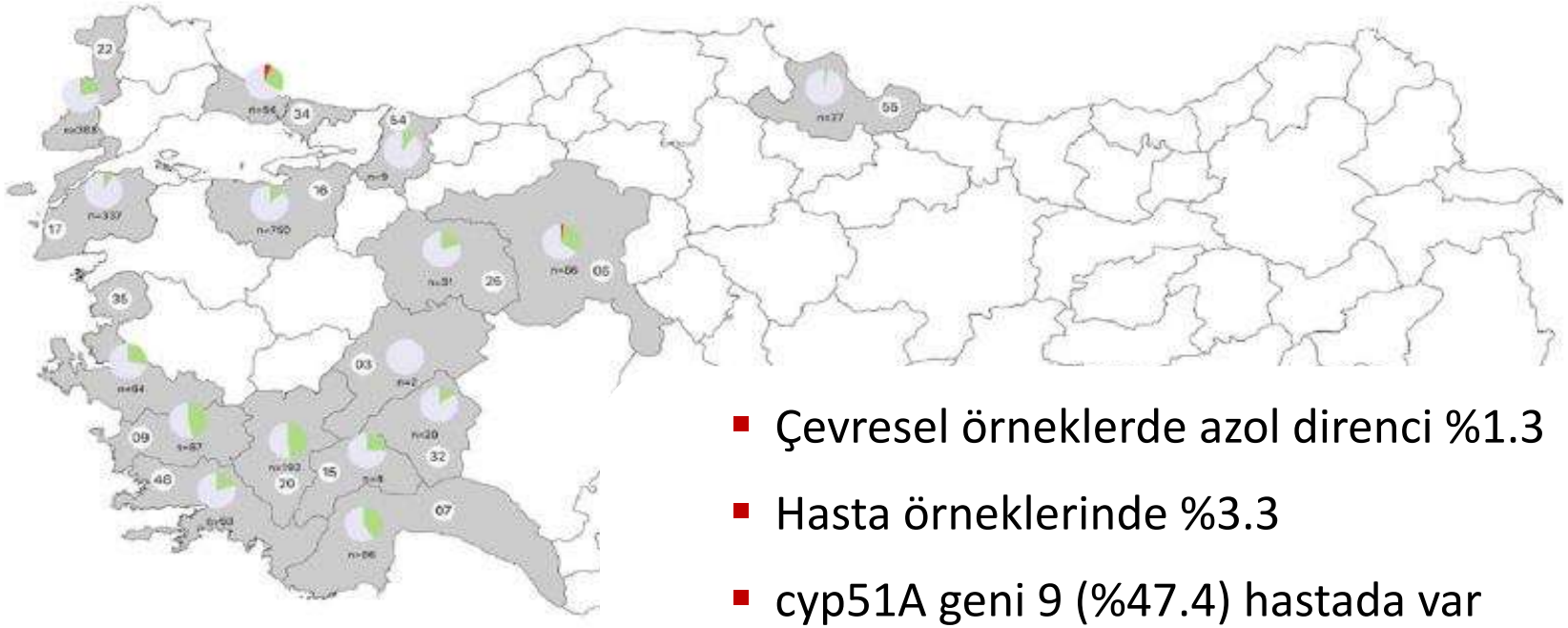


Figure 1. Distribution of participating centres. The grey c
indicates the growth percentage of that sample, while th
in black and white in the print version of *JAC*.

- Çevresel örneklerde azol direnci %1.3
- Hasta örneklerinde %3.3
- cyp51A geni 9 (%47.4) hastada var
- *A. fumigatus* azol direnç oranı düşük

Neofytos *et al. BMC Infectious Diseases* (2021) 21:296
https://doi.org/10.1186/s12879-021-05958-3

BMC Infectious Diseases

GUIDELINES Open Access

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

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]

Yoğun Bakım Ünitelerinde İA

- YBÜ'de genel infeksiyon yükünün %1,4'ü
- Otopsi çalışmaları,
  - İPA insidansı ~ %1-3,5
  - ARDS varsa %12,5'e ulaşır
- Hematolojik olmayan YBÜ hastalarında ölüm oranı %4

JAMA 2009; 302: 2323–2329.
Infect Dis Clin N Am 2017: 31; 475-487
Semin Respir Crit Care Med 2019;40:540–547.
Medical Mycology, 2022, Vol. 60, No. 1

Biyolojik İlaç Kullanımı ve İA

- TNF-α inhibitörü
  - Infliximab
  - Adalimumab
  - Etanercept
  - Certolizumab pegol
  - Golimumab
    - İnsidansının 6,19- 8,63 vaka/100.000
- Ibrutinib ve küçük molekül ağırlıklı diğer tirozin kinaz inhibitörleri
- CD inhibitörleri
  - Alemtuzumab
  - Basiliximab
  - Daclizumab
  - Rituximab

Infect Dis Clin N Am 34 (2020) 389–411

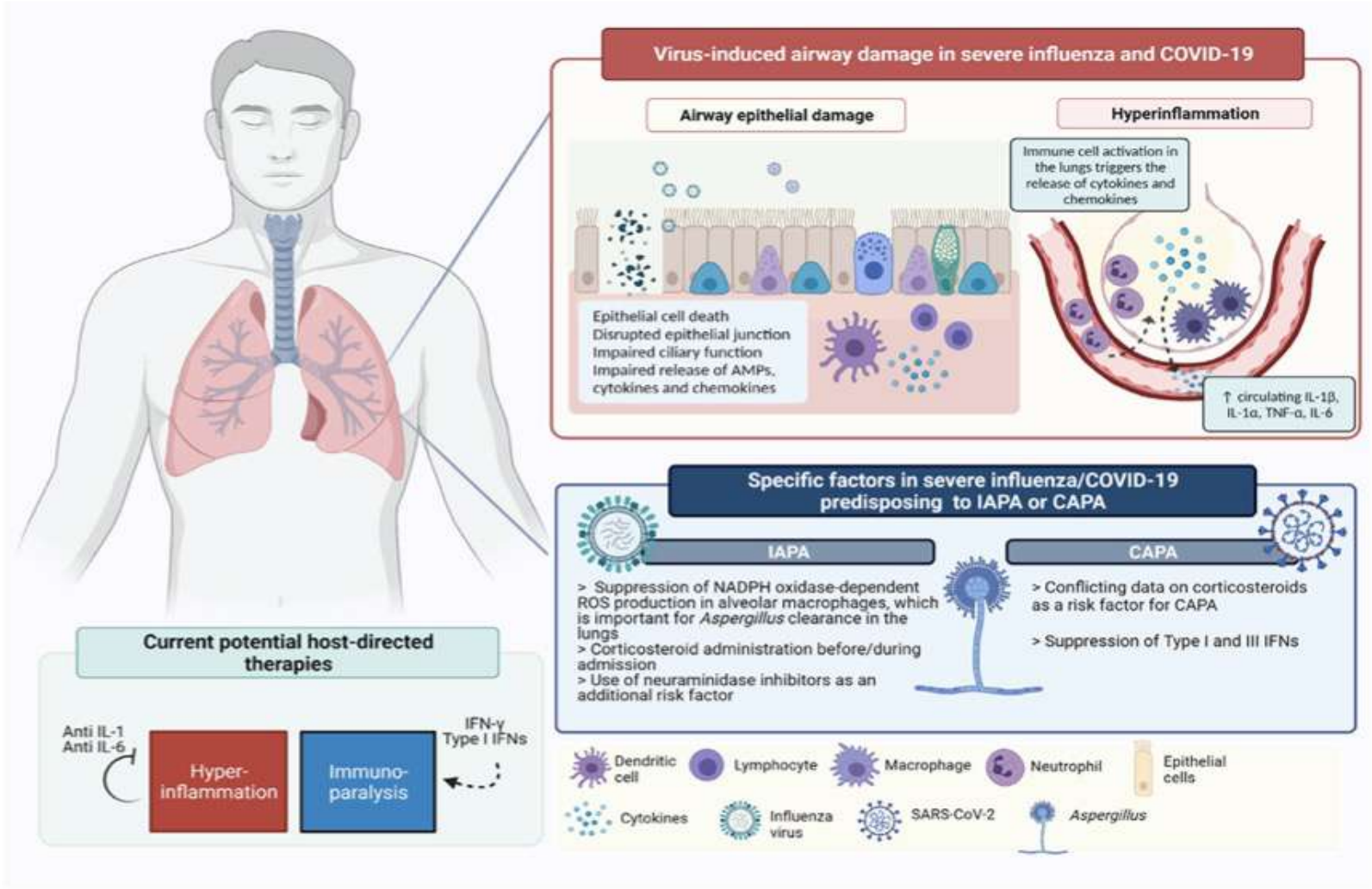
Available online at www.sciencedirect.com

ScienceDirect

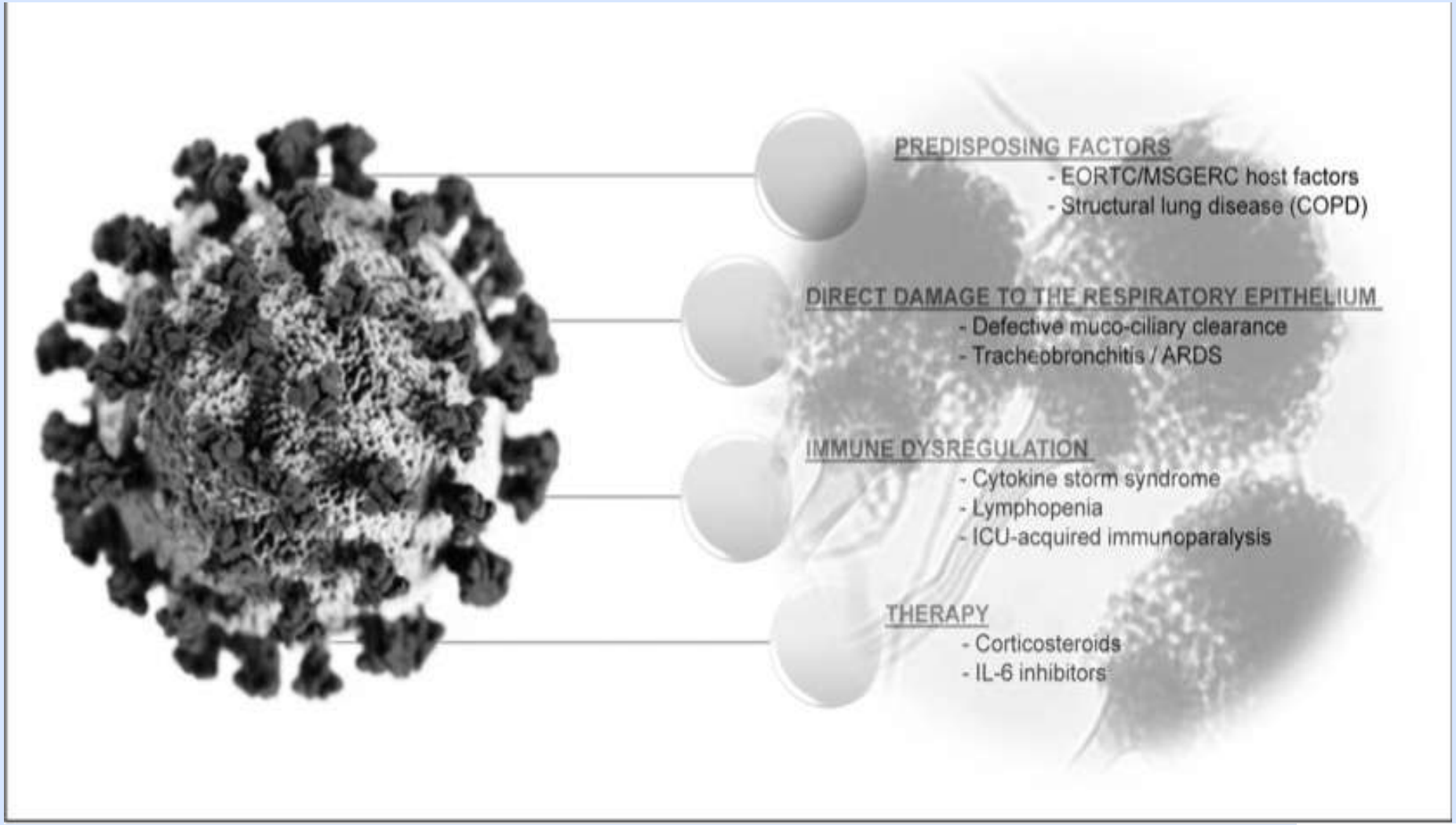
Current Opinion in Microbiology

Invasive pulmonary aspergillosis associated with viral pneumonitis

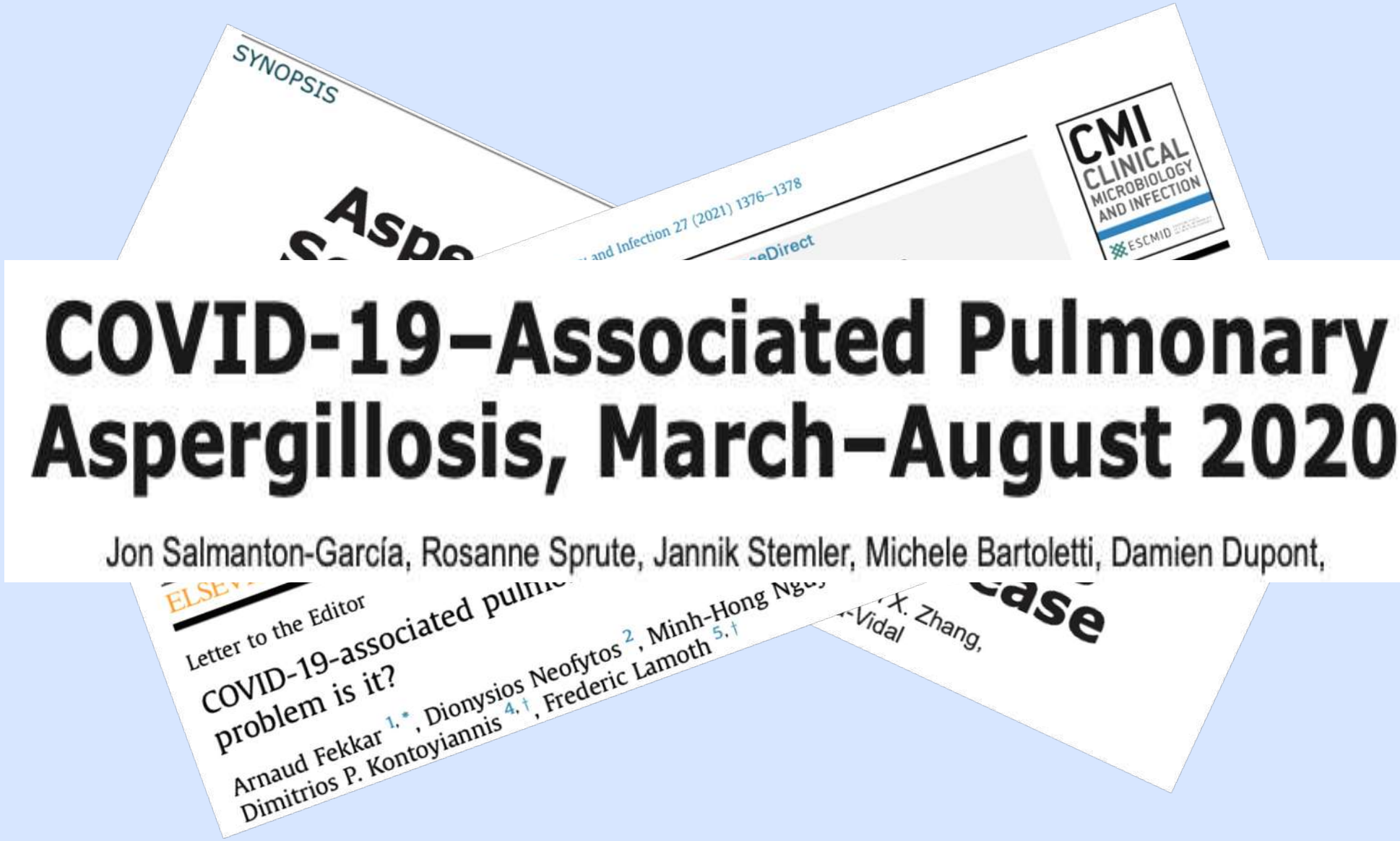
Intan MW Dewi[1,3,6,7], Nico AF Janssen[1,6,7], Diletta Rosati[1,6],



COVID-19 İlişkili Pulmoner Aspergilloz (CAPA) Patogenezi



Curr Opin Crit Care 2022, 28:470 – 479



COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont,

COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont,

- Retrospektif
  - FungiScope kayıtları ve literatür
- 17 ülke, 186 CAPA
  - Ortanca yaş 68 (15–87)
  - %72,6 erkek
- CAPA insidansı
  - Kümülatif %6,9
  - YBÜ'de %1,0-%39,1
- Mortalite
  - Genel % 52,2
  - CAPA'ya bağlı %33

Emerg Infect Dis 2021; **27:** 1077–86.

COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont,

Table 1. Pathogens of 186 patients with coronavirus disease–associated pulmonary aspergillosis, March–August 2020*

Characteristic	No. (%)
Pathogens†	
Aspergillus fumigatus	122 (65.6)
A. niger	13 (7.0)
A. flavus	10 (5.4)
A. terreus	6 (3.2)
A. calidoustus	1 (0.5)
A. lentulus	1 (0.5)
A. nidulans	1 (0.5)
A. penicillioides	1 (0.5)
A. versicolor	1 (0.5)
A. tubingensis	1 (0.5)
Aspergillus spp. (culture)‡	1 (0.5)
Aspergillus spp. (serologic techniques)	34 (18.3)
Other pathogens§	40 (21.5)

Emerg Infect Dis 2021; **27:** 1077–86.

Clinical Infectious Diseases
MAJOR ARTICLE

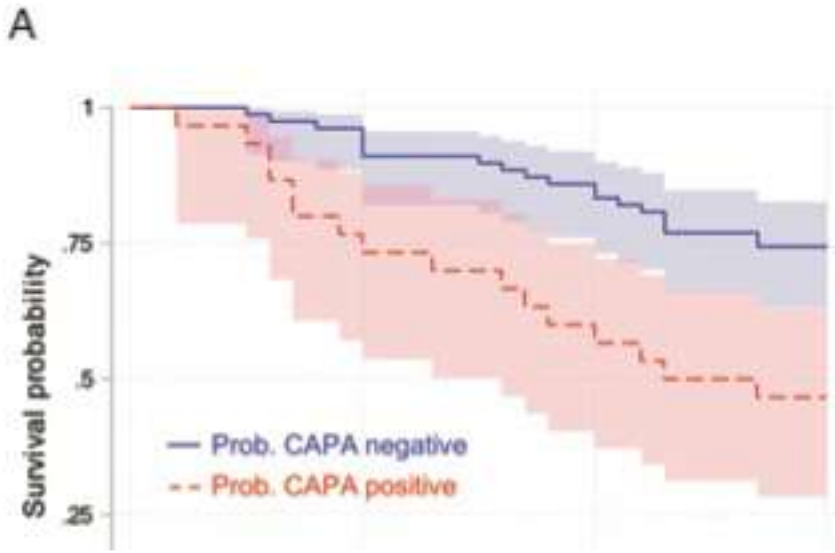
Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study

Michele Bartoletti,[1,©] Renato Pascale,[1] Monica Cricca,[2] Matteo Rinaldi,[1] Angelo Maccaro,[1] Linda Bussini,[1] Giacomo Fornaro,[1] Tommaso Tonetti,[3]

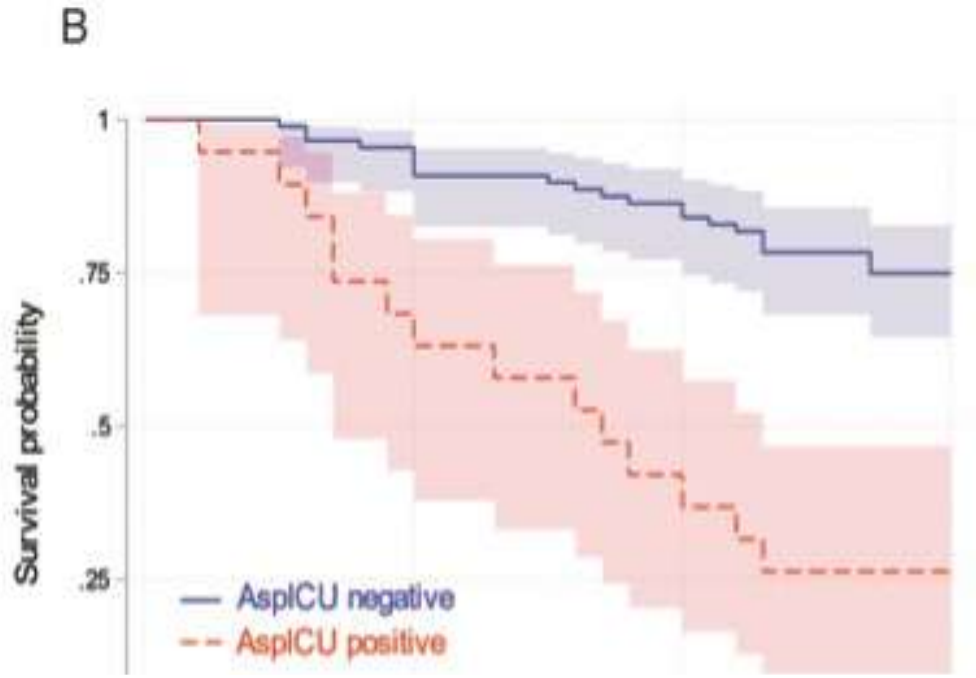
- Prospektif, çok merkezli
- 108 hasta
  - Doğrulanmış COVID-19
  - Mekanik ventilasyon
- İA için tarama portokolü
  - Bronkoalveoler lavaj
  - Galaktomannan
- 30 (%27,7) "olası" CAPA
- 19 (%17,6) PIPA
  - AspICU algoritması ile

Clinical Infectious Diseases 2021;73(11):e3606–14

YBÜ kabulden sonraki 30 günlük mortalite için Kaplan-Meier sağkalım eğrileri



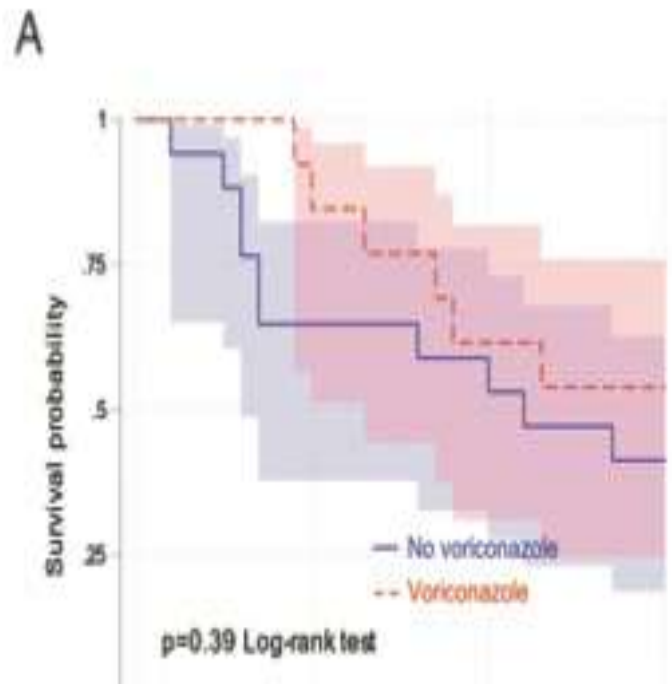
- Mortalite
  - CAPA olan hastalarda %44
  - CAPA olmayan hastalarda %19
    - P = .002



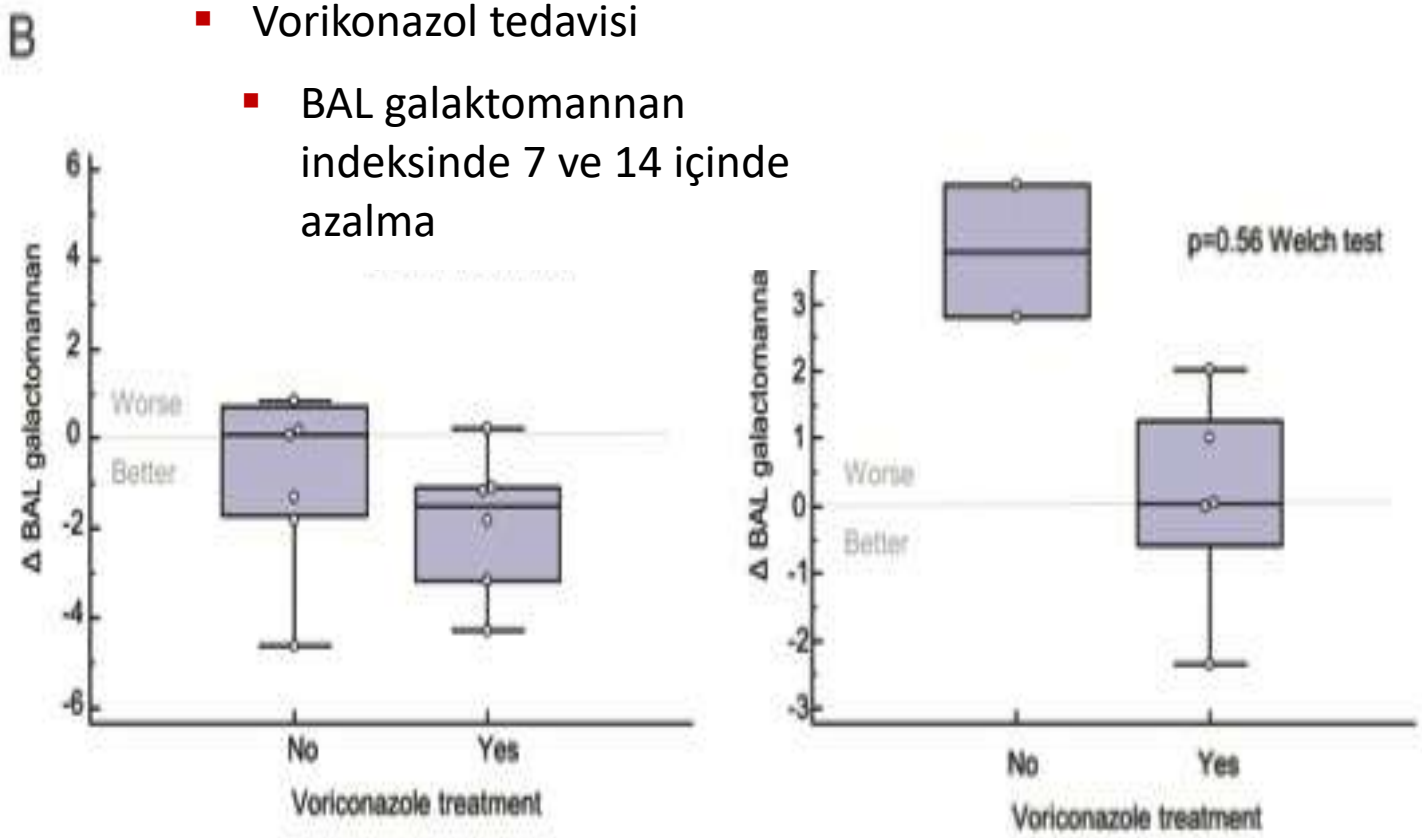
- Mortalite
  - PIPA olan hastalarda %74
  - CAPA olmayan hastalarda %26
    - P < .001

Clinical Infectious Diseases 2021;73(11):e3606–14

Olası CAPA'lı hastalarda vorikonazol tedavisinin etkisi



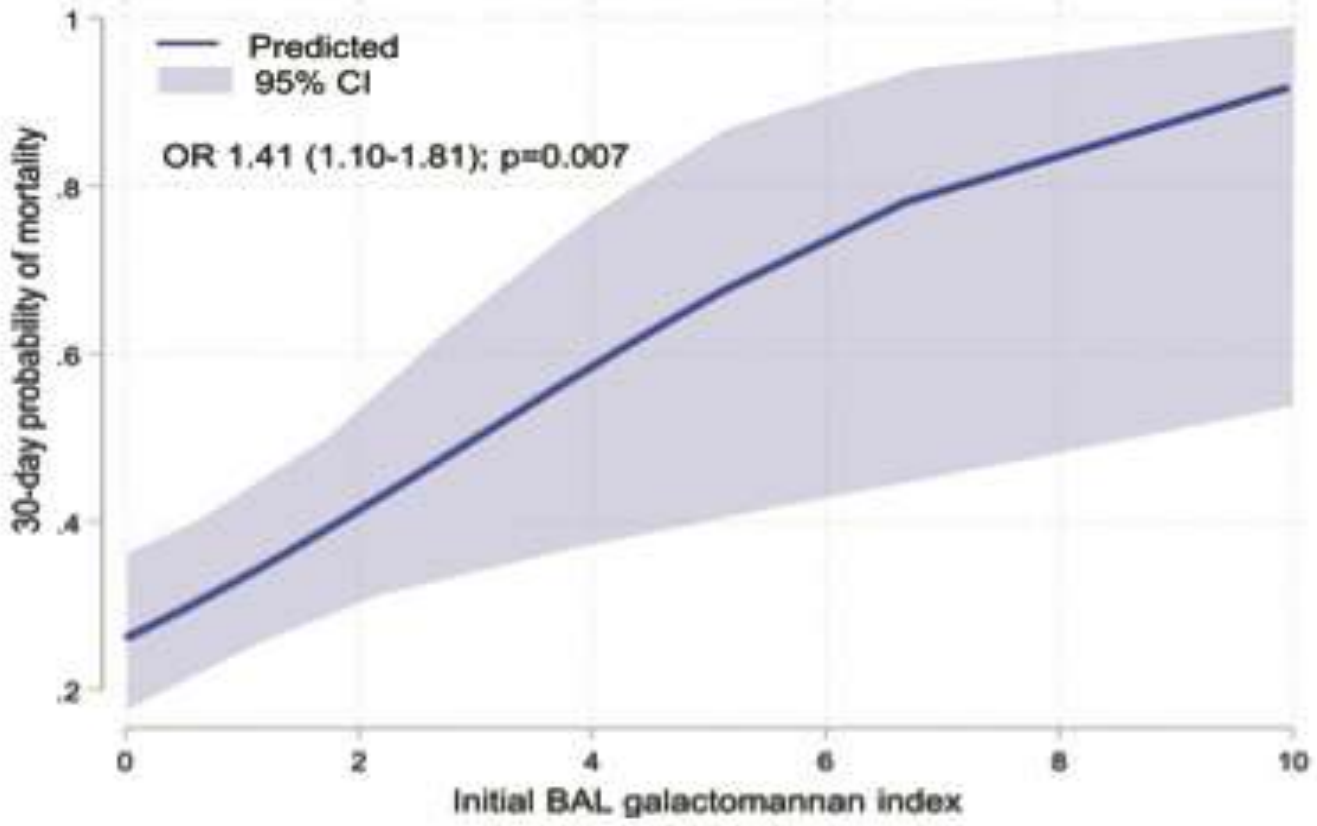
- Vorikonazol tedavisi daha düşük mortalite ile ilişkili
  - %46 vs %59; P = .30



- Vorikonazol tedavisi
  - BAL galaktomannan indeksinde 7 ve 14 içinde azalma

Clinical Infectious Diseases 2021;73(11):e3606–14

BAL galaktomannan indeksi ile 30 günlük mortalite ilişkisi



- Düşük BAL galaktomannan indeksi
- Daha yüksek sağ kalım

İA Risk Faktörleri

Infect Dis Clin N Am 30 (2016) 125–142

Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Organ Nakli Alıcılarında İnvaziv Aspergilloz İçin Risk Faktörleri

Karaciğer nakli

- Erken (0-3 ay)
  - Yeniden transplantasyon
  - Böbrek yetmezliği
  - Fulminan hepatit
  - MELD>30
- Geç (>3 ay)
  - CMV infeksiyonu
  - Kreatinin>3,3g/dL

Akciğer nakli

- Tek akciğer nakli
- Erken hava yolu iskemisi
- CMW infeksiyonu
- Rejeksiyon ve artırılmış immünsupresyon
- Aspergillus kolonizasyonu
- İntraoperatif pozitif Aspergillus kültürü
- Hipogamaglobulinemi (IgG<400mg/dL)

Böbrek nakli

- Nakil öncesi KOAH
- Son 3 ayda akut rejeksiyon
- Greft yetmezliği
- Kortikosteroidler

Kalp nakli

- *Aspergillus* kolonizasyonu
  - YBÜ'de havadaki Aspergillus sporları
  - Yeniden ameliyat
  - CMV hastalığı
  - Nakil sonrası hemodiyaliz
  - İki ay öncesi veya kalp nakli sonrası IA epizodu

Clinical Transplantation. 2019;33:e13544.

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2022, 60, myab064
https://doi.org/10.1093/mmy/myab064
Advance Access Publication Date: 22 October 2021
Review Article

Review Article

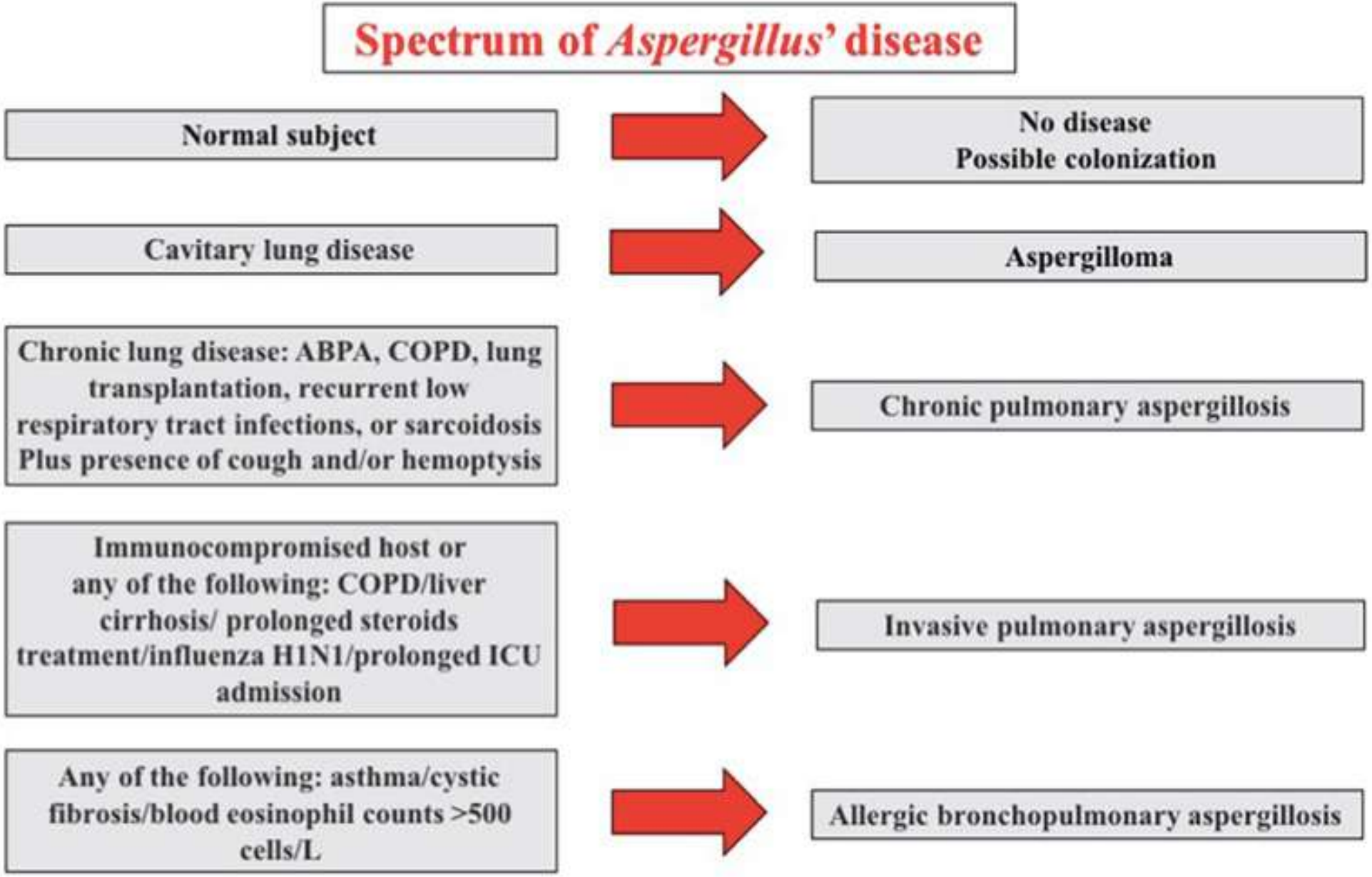
Aspergillosis: Emerging risk groups in critically ill patients

Stefan Kluge [1,*], Richard Strauß [2], Matthias Kochanek [3], Markus A. Weigand [4],

Table 1. Risk factors for IA in non-neutropenic ICU patients.

Risk factor
•Prolonged corticosteroid treatment
•Chronic obstructive pulmonary disease (COPD)
•Advanced (decompensated) liver cirrhosis with a duration of stay in the ICU longer than 7 days
•Solid tumors requiring admission to the ICU
•HIV infection
•Solid organ (esp. lung) transplantation
•Systemic diseases requiring immunosuppressive therapy
Underlying conditions causing an immunocompromized status or immunosuppression
• Influenza
• COVID-19
• Sepsis
• Concentration of *Aspergillus* spores in the air
• Diabetes
• Alcoholism
• Malnutrition
• Lifestyle: Smoking tobacco or marijuana, body piercing, tattooing, intravenous drugs use

Spectrum of *Aspergillus*' disease



Infect Dis Ther (2020) 9:511–524

İPA Olgu Tanımları
EORTC/MSGERC

Table 1. Invasive pulmonary aspergillosis case definitions for critically ill patients

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*	-

Curr Opin Crit Care 2022, 28:470 – 479

İPA Olgu Tanımları
*Asp*ICU

*Asp*ICU (2)	**Proven IPA**	-	-	*Same as EORTC/MSGERC*
		Entry criterion: Positive culture of lower respiratory tract specimen		
	Putative IPA	**Compatibles signs/symptoms:** Fever despite antibiotics >3d or recrudescent after 48h defervescence, dyspnea, hemoptysis, chest pain, pleuritic rub, worsening respiratory insufficiency **± Host risk factors:** Neutropenia, chemotherapy, corticosteroids>20mg/d, congenital or acquired immunodeficiency	**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
	***Aspergillus* colonization**	≥1 criterion for putative IPA is not met		
Modified *Asp*ICU (3)	**Proven IPA**	-	-	*Same as EORTC/MSGERC*
	Putative IPA	**Compatibles signs/symptoms:** *Same as AspICU*	**Chest X-ray or CT scan:** *Same as AspICU*	At least 1: • Positive culture of BAL • BAL GM ≥1 • Serum GM ≥0.5

Curr Opin Crit Care 2022, 28:470 – 479

İnfluenza İlişkili Pulmoner Aspergilloz (İAPA) Olgu Tanımları

Table 1. *(Continued)*

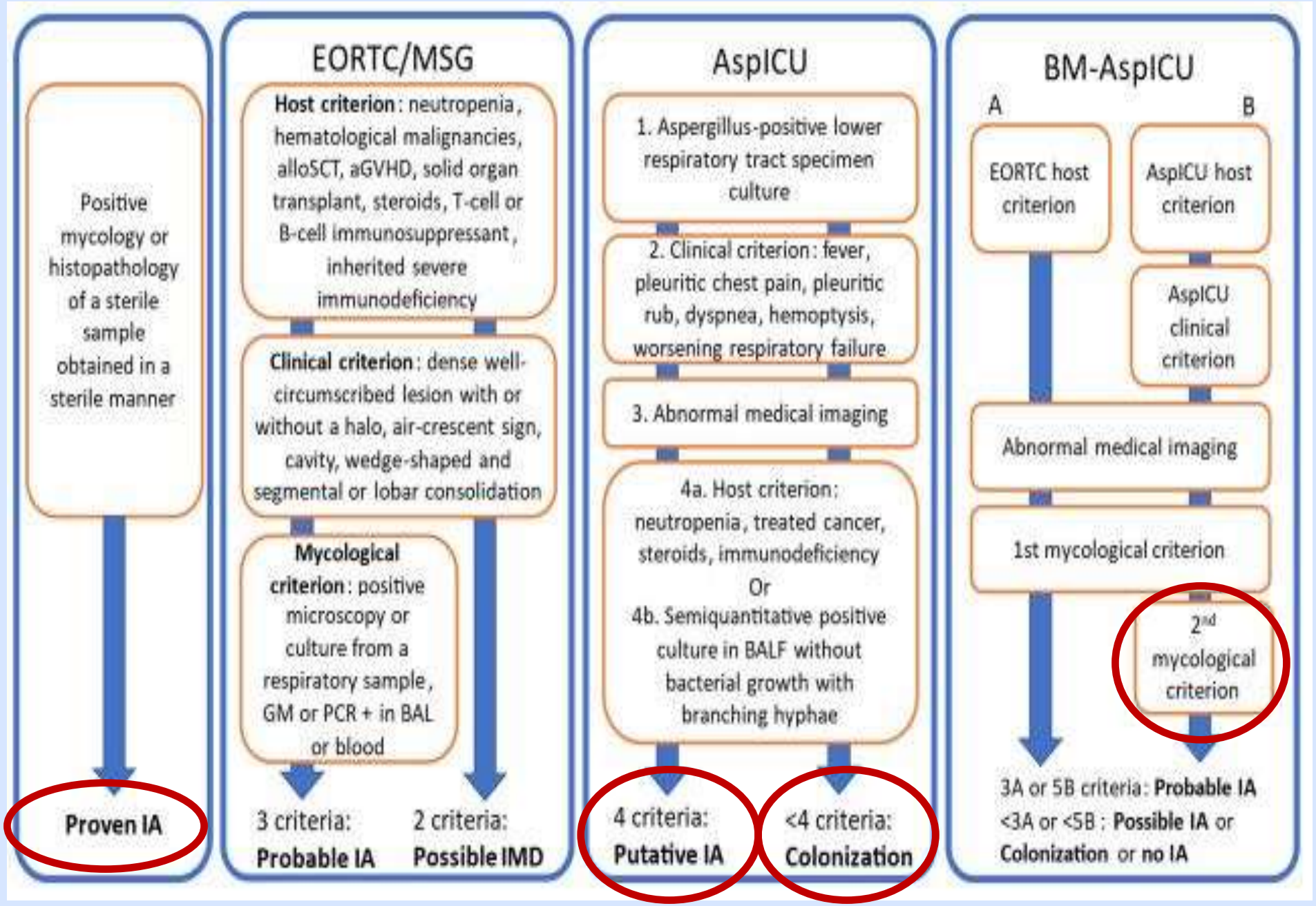
Criteria		Clinical	Radiological	Mycological
		Entry criterion: ICU admission for respiratory distress with a positive influenza test		
Expert case definitions for IAPA (4)	Proven IAPA / *Aspergillus* tracheobronchitis	-	-	**Lung biopsy**, at least 1. • Histo/cytopathologic or direct microscopic examination (hyphae) • Positive culture or PCR from tissue
	Probable IAPA	-	**Chest X-ray or CT scan:** Pulmonary infiltrate	At least 1: • Positive culture of BAL • Serum GM >0.5 or BAL GM ≥1
		-	**Chest X-ray or CT scan:** Cavitating infiltrate (with no other cause)	At least 1: • Positive culture of tracheal aspirate • Positive culture of sputum
	Aspergillus tracheobronchiti	**Bronchoscopic examination:** airway plaque, pseudomembrane, or ulcer		At least 1: • Serum GM > 0.5 or BAL GM ≥1 • Positive culture of BAL, tracheal aspirate or sputum • Positive direct microscopy (hyphae)

Curr Opin Crit Care 2022, 28:470 – 479

Covid -19 İlişkili Pulmoner Aspergilloz (CAPA) Olgu Tanımları ECMM/ISHAM

		Entry criterion: ICU admission for COVID-19		
ECMM/ISHAM case definitions for CAPA (5)	**Proven CAPA (pulmonary or tracheobronchial form)**	-	-	**Lung biopsy**: Histopathologic or direct microscopic examination (hyphae + tissue damage) or positive culture/PCR from tissue
	Probable CAPA (pulmonary form)	Refractory fever, pleural rub, chest pain, hemoptysis	**Chest X-ray or CT scan:** • Pulmonary infiltrate • Cavitating infiltrate	At least 1: • Positive direct microscopy of BAL (hyphae) • Positive culture of BAL • Serum GM >0.5 or BAL GM ≥1 • Positive *Aspergillus* PCR in serum *x2* or BAL *x1* (<36 cycles) or serum + BAL *x1*
	Probable CAPA (tracheobronchial form)	**Bronchoscopic examination:** airway ulceration, nodule, pseudomembrane, plaque or eschar		At least 1: • Positive direct microscopy of BAL (hyphae) • Positive culture of BAL • Serum GM >0.5 or BAL GM ≥1 • Positive *Aspergillus* PCR in BAL *x1*
	Possible CAPA	*Same as probable CAPA*	*Same as probable CAPA*	At least 1: • Positive direct microscopy of NBL (hyphae) • Positive culture of NBL • NBL GM >4.5 *x1* or >1.2 *x2* • NBL GM >1.2 + positive *Aspergillus* PCR in NBL

Curr Opin Crit Care 2022, 28:470 – 479



Fungi **2023, 9, 131. https://doi.org/10.3390/jof9020131**

İA'da Tanı Güç

- Rutin antifungal profilaksi
- Erken empirik tedavi
  - Gereksiz antifungal ilaç tedavisi
  - İlaç yan etkisi
  - Artan sağlık bakımı giderleri

- Empirik → Pre-emptive
  - Duyarlı ve hızlı serolojik testlerle *Aspergillus* antijenlerinin saptanması
  - Genomik DNA dizilerinin saptanması
  - Tıbbi görüntüleme

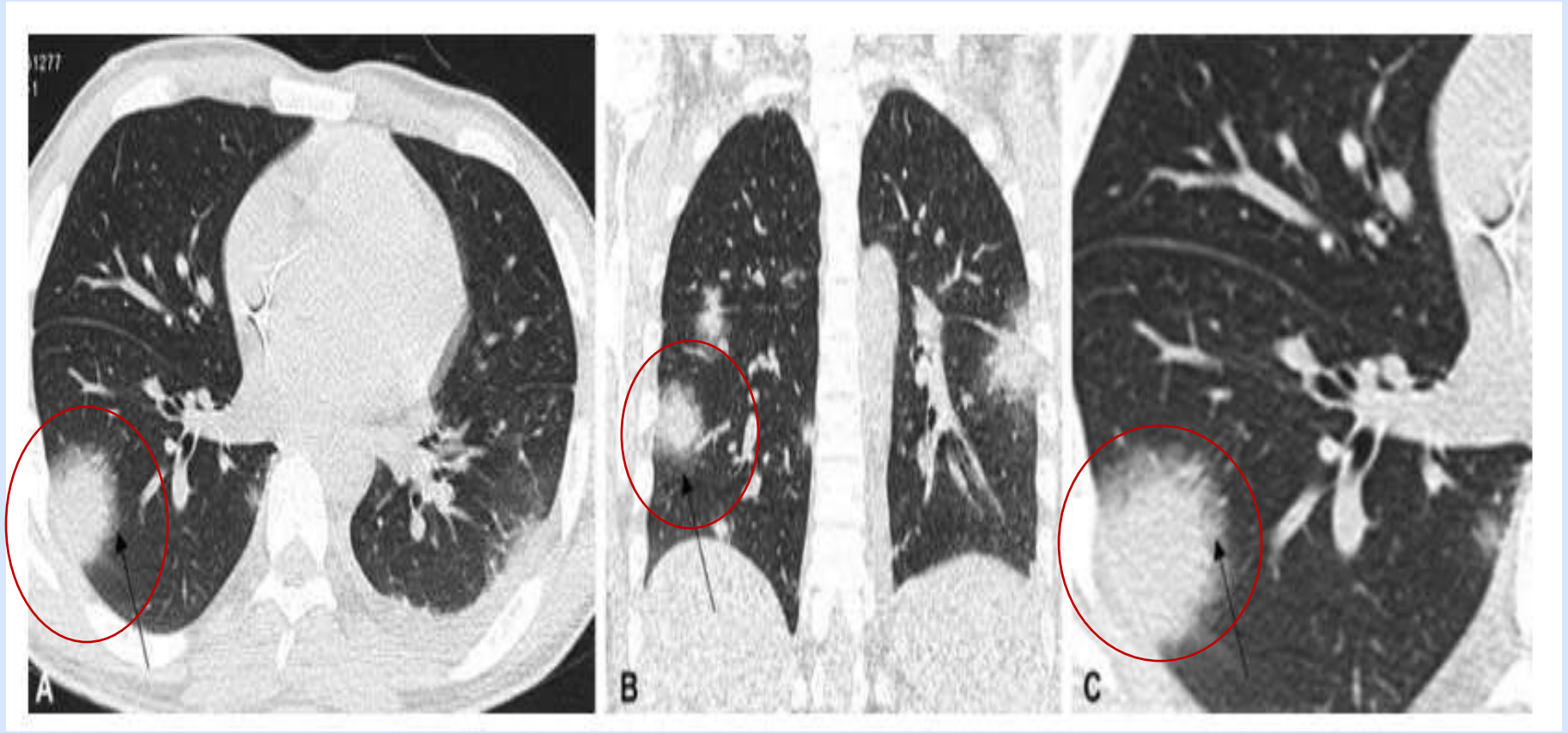
Decoding the Guidelines of Invasive Pulmonary Aspergillosis in Critical Care Setting: Imaging Perspective

Table 2 Comparison of pathological and radiological manifestations of IPA in neutropenic and non-neutropenic patients[22]

Categories of ICU patients	Neutropenic patients	Non-neutropenic immunosuppressed/ critically ill immunocompetent patients
Pathophysiology	*Aspergillus* becomes angioinvasive within hours	Prolonged airway invasive phase prior to angioinvasion
Pathology	Lung lesions represent coagulative necrosis, hemorrhagic infarction, and angioinvasion	Lung lesions represent pyogranulomatous inflammation and necrosis with no angioinvasion initially
Radiology	Typical findings: • Scattered nodules most common • Peripheral GGO halo • Air crescent • Hypodense sign • Peripheral wedge-shaped infarcts and consolidations	Atypical findings: • Tracheal/bronchial wall thickening (large airways) • Tree-in-bud opacities (small airways) • Consolidations and nodules ± cavitation and GGOs with predominant peribronchial distribution (most common) • Nonspecific infiltrates (most common)
Microbiology	Serum galactomannan (GM) positivity	Serum GM unreliable (prolonged airway invasive phase)

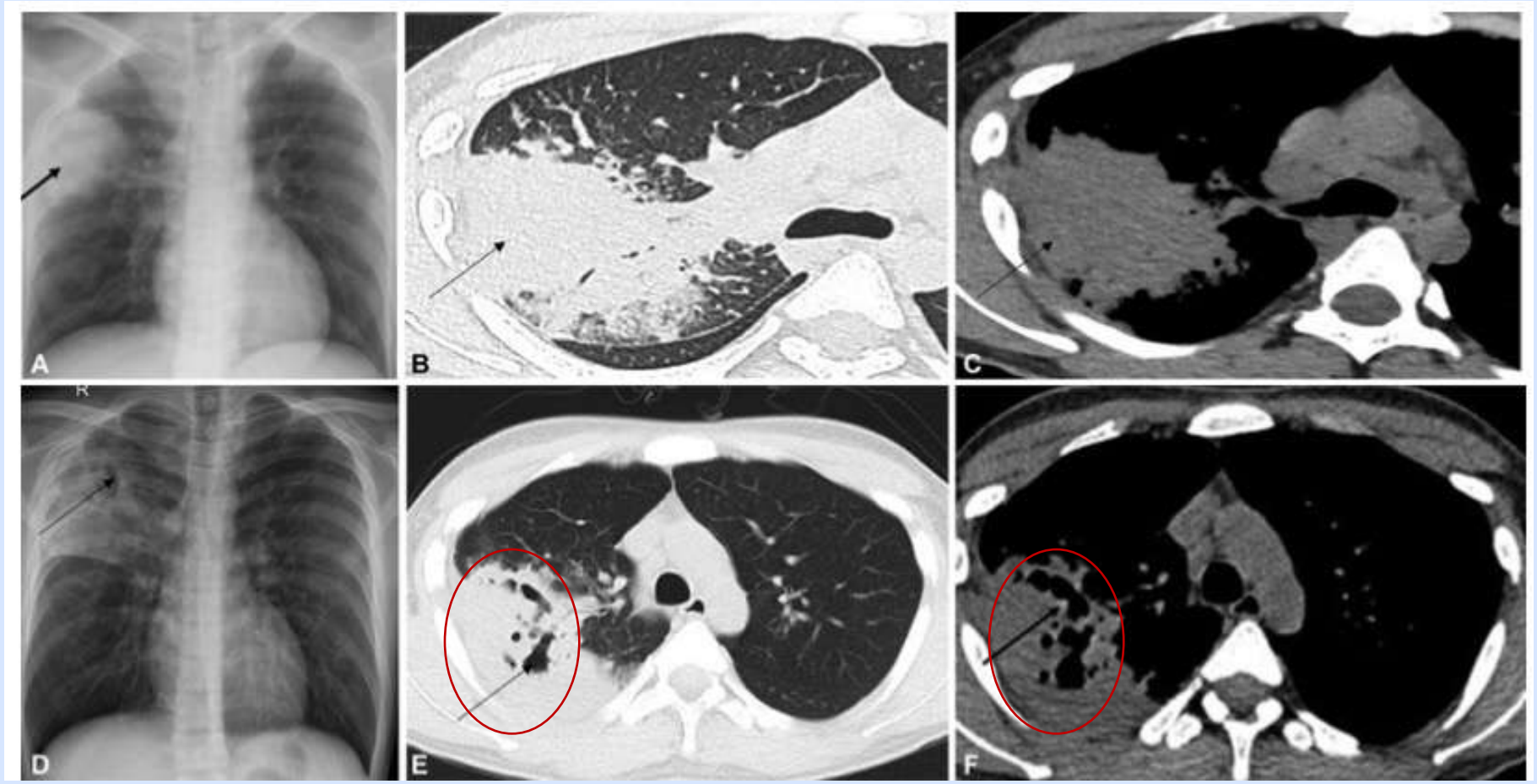
Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.

“Halo” İşareti



Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.

“Hava-hilal” İşareti



Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.

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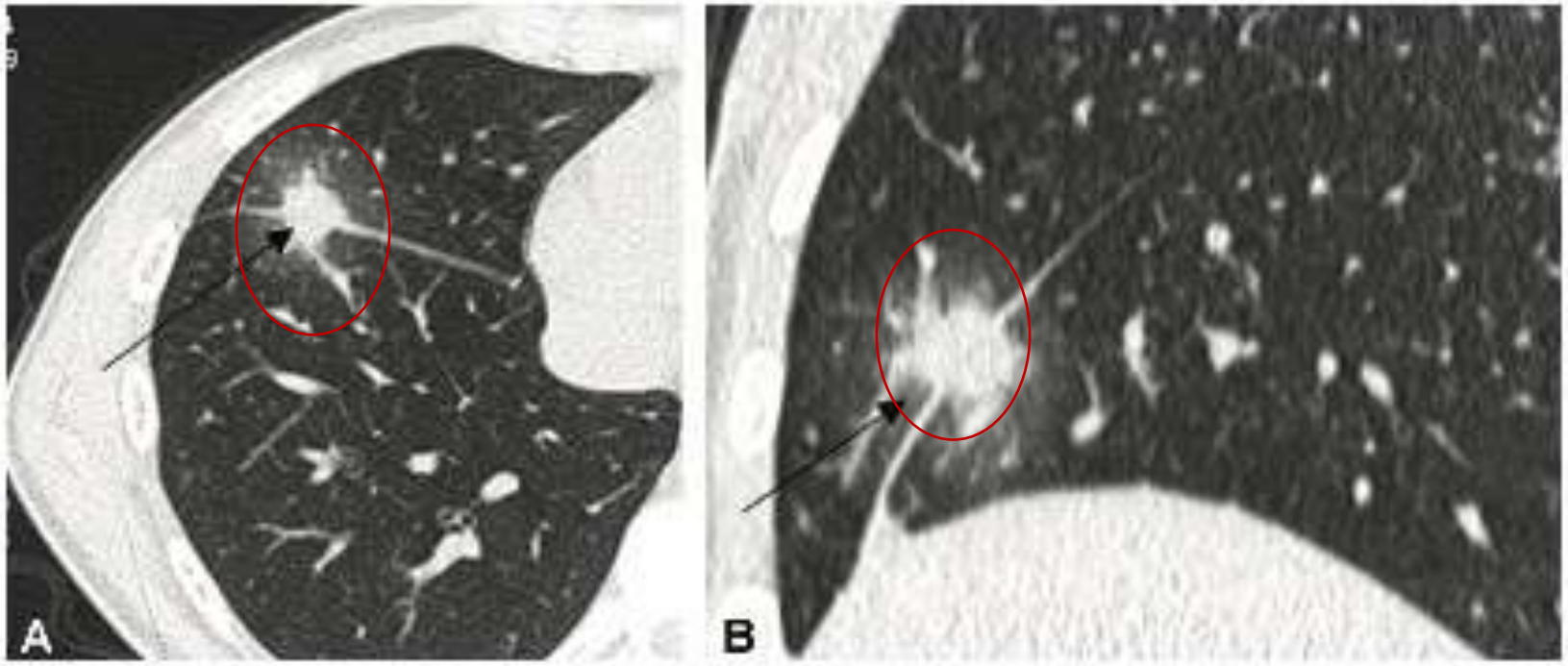
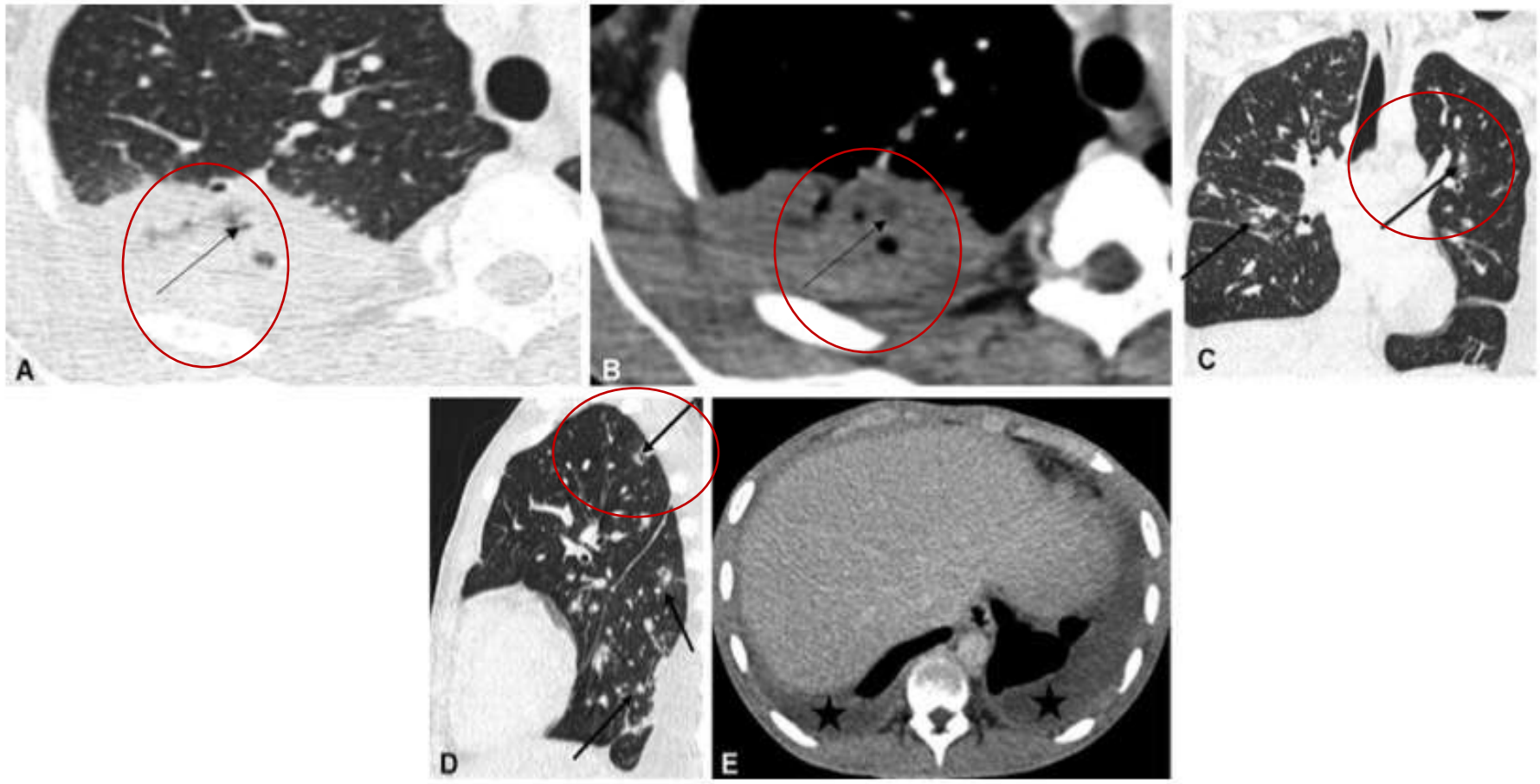


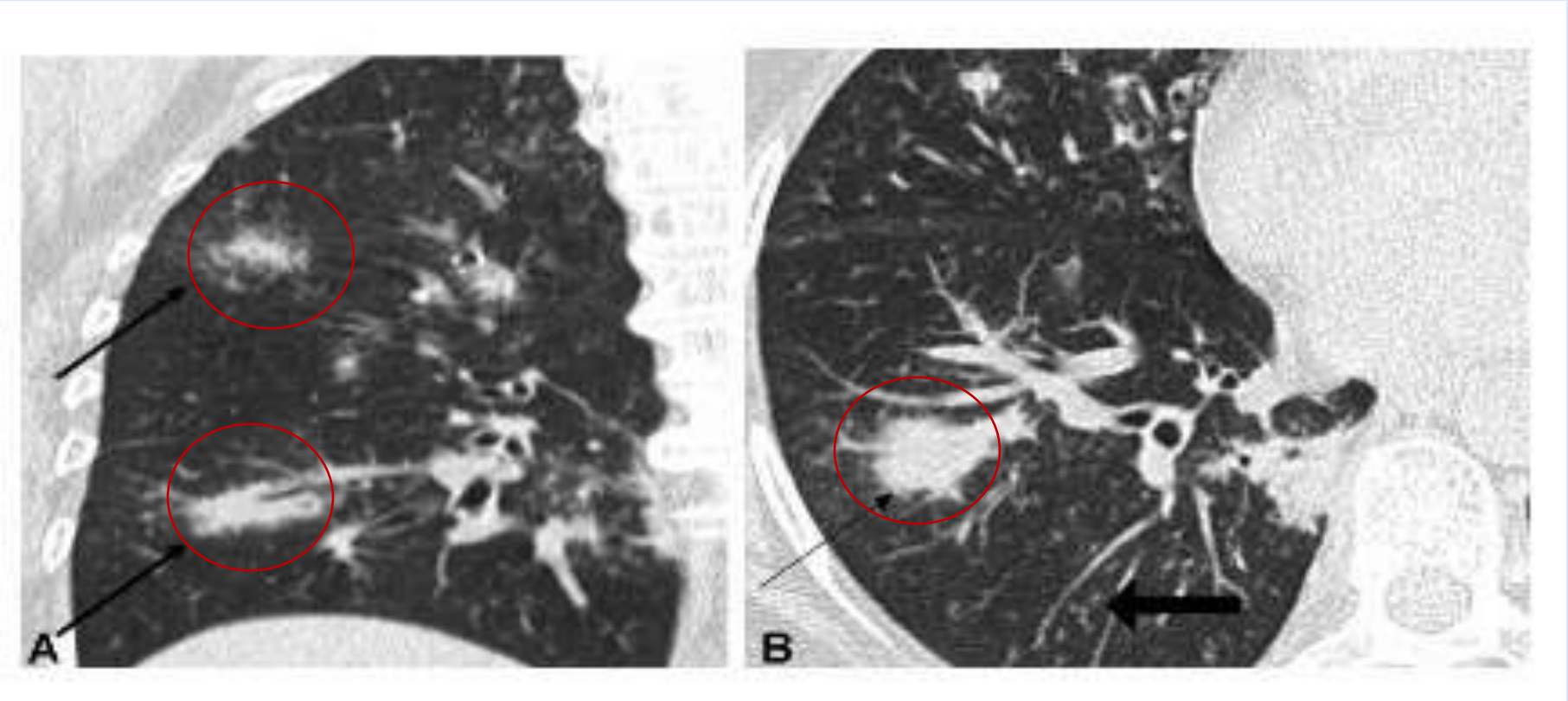
Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.

İnfarkt benzeri periferik konsolidasyon



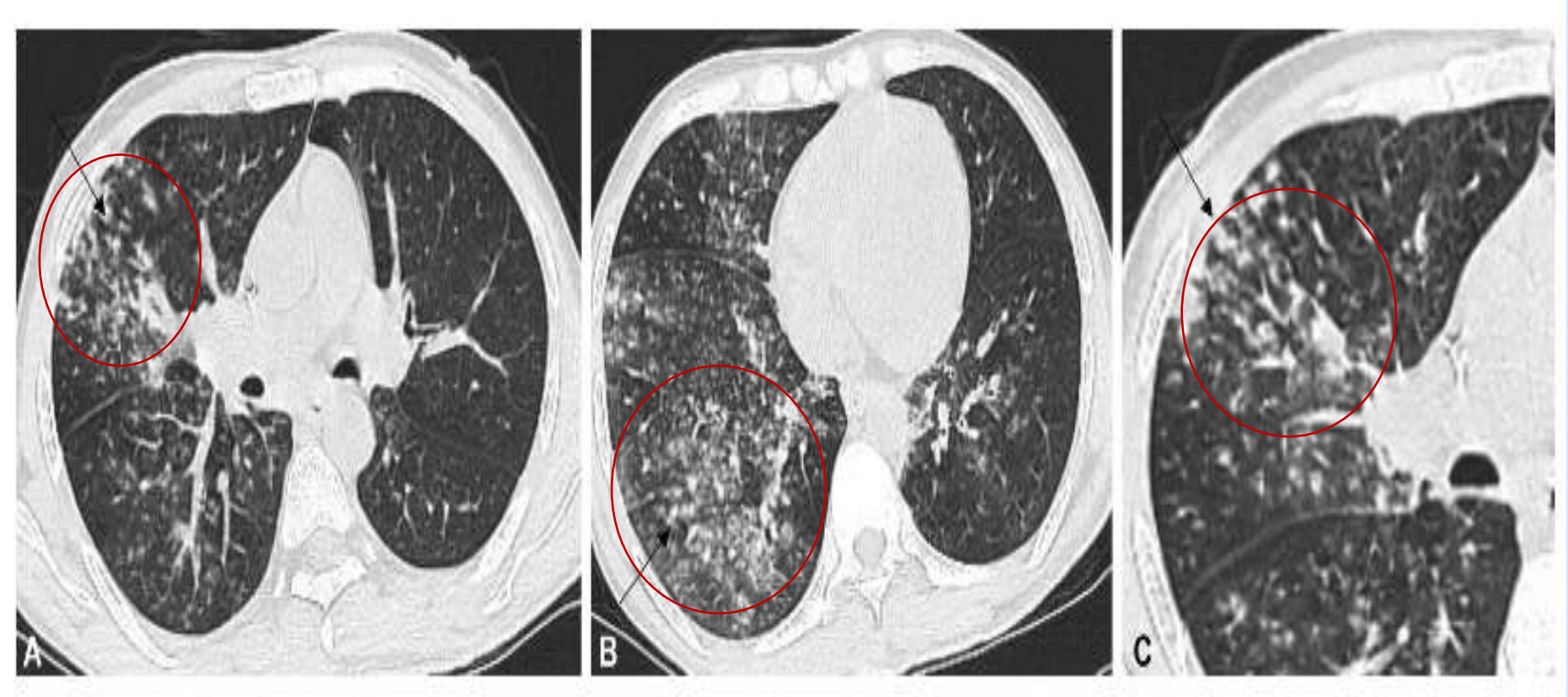
Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.

Bronkopnömoni

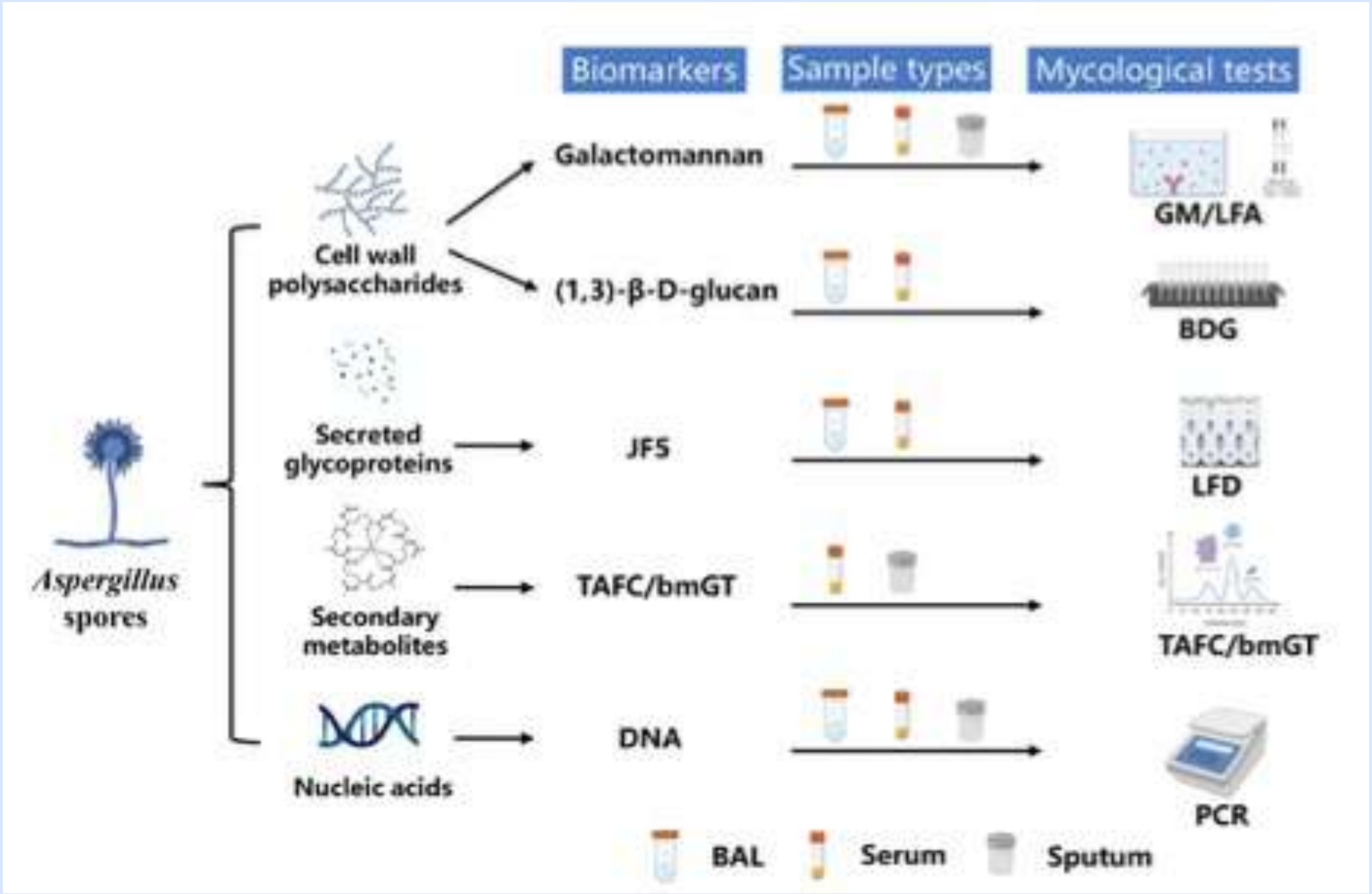


Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.

“ Tomurcuklanmış ağaç” Paterni



Indian J Radiol Imaging. DOI https://doi.org/ 10.1055/s-0043-57004.



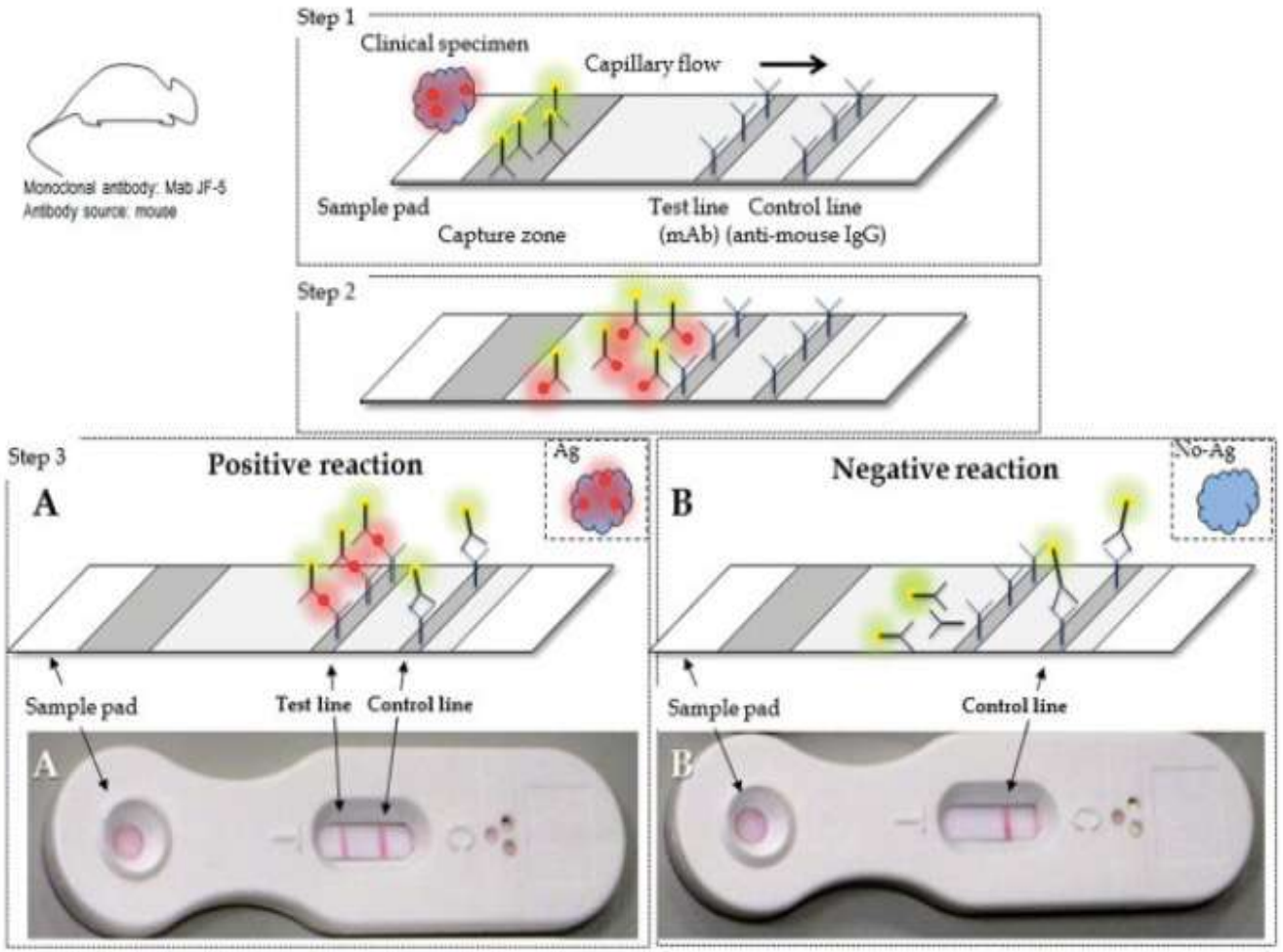
*Liu M, et al. BMJ Open 2022;**12**:e057746.*

İA'da Monoklonal Antikora Dayalı Tanısal Yaklaşımlar

- Lateral-flow Device
- İmmünohistokimya veya immünofloresan yöntemi
- Biyolüminesans Görüntüleme
- Immune PET/MRI

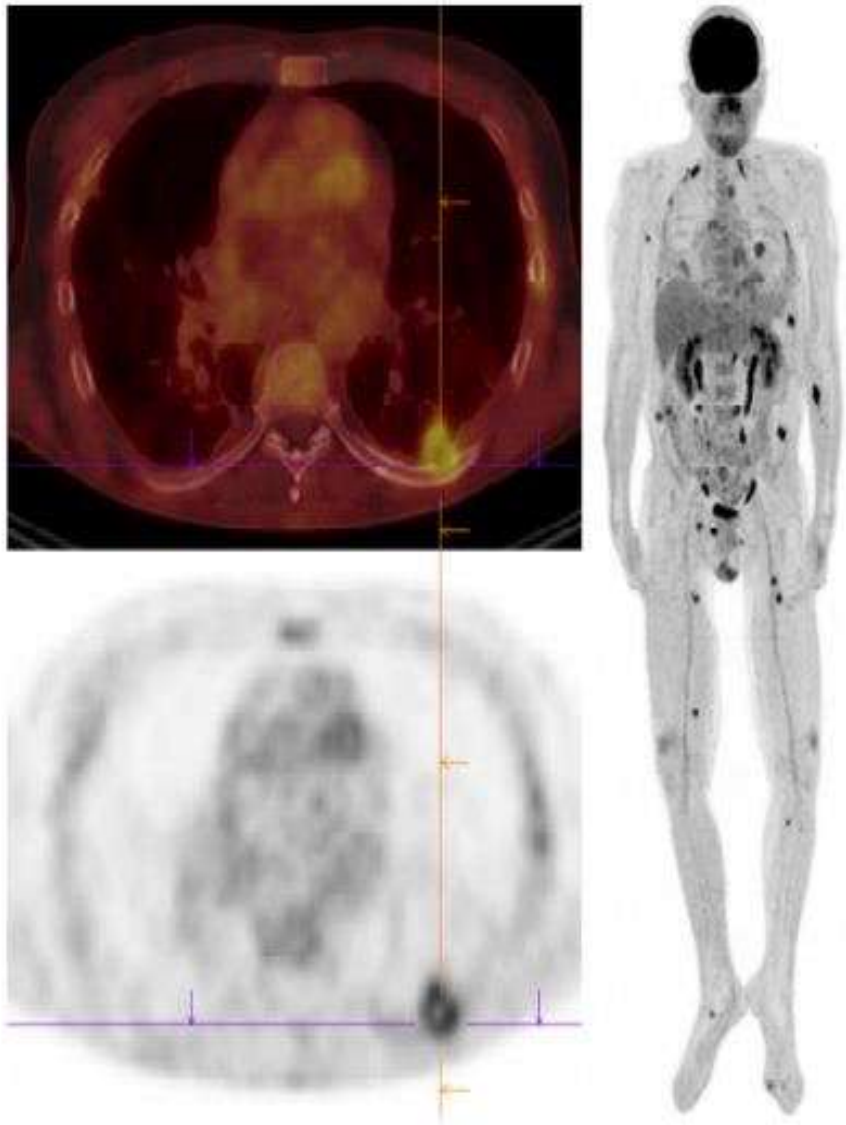
Int. J. Mol. Sci. **2022, 23, 5563. https://doi.org/**10.3390/ijms23105563

“Lateral-flow Device”



LFD testi

- *Aspergillus t*ürleri için spesifik bir monoklonal antikor kullanır
  - Fare JF5 monoklonal antikoru
- Hızlı (15 dakika)
- Ucuz



- SOT hastası
- BT taraması ile birleştirilmiş pozitron emisyon tomografisi (PET-BT)

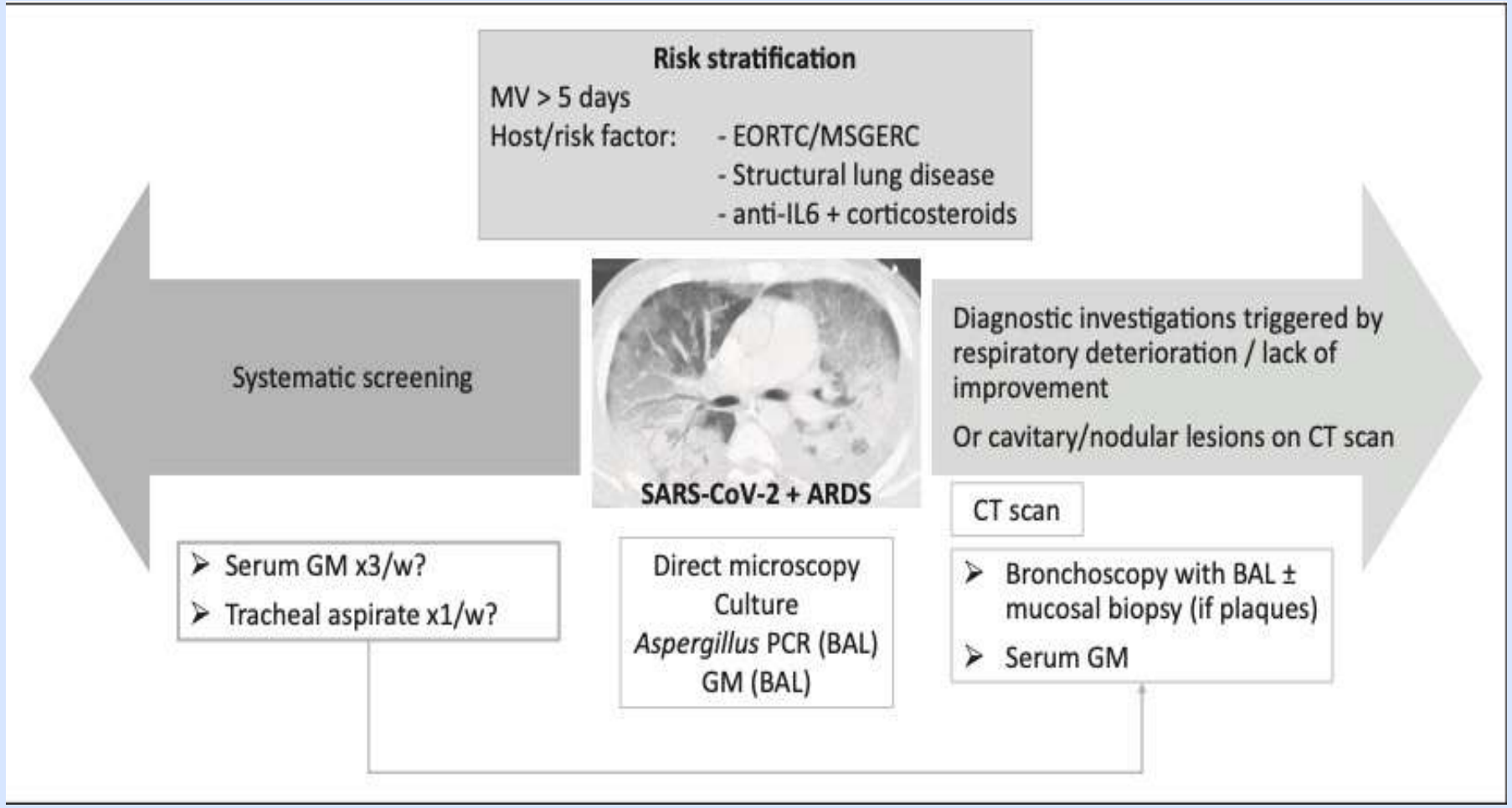
Fungi 2023, 9, 131. https://doi.org/10.3390/jof9020131

İA Tanı

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.***

YBÜ'de CAPA İçin Tanı Stratejisi



Curr Opin Crit Care 2022, 28:470 – 479

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]

Haematologica 2017
Volume 102(3):433-444

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

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]

Haematologica 2017
Volume 102(3):433-444

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.

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,

Clinical Microbiology and Infection 24 (2018) e1–e38

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	

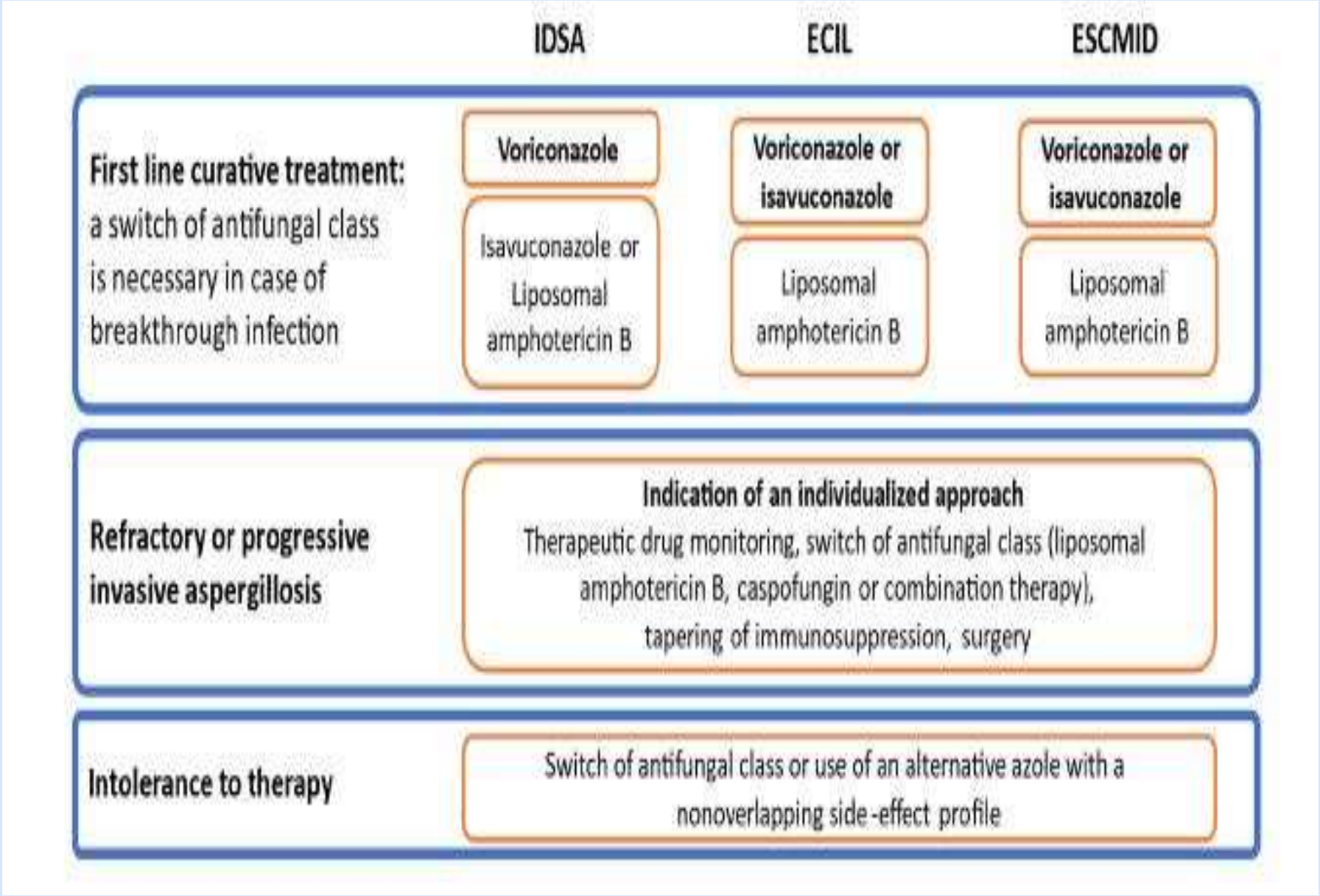
SUPPLEMENT ARTICLE

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

Abby P. Douglas,[1,2,3,4] Olivia. C. Smibert,[1,2,3,4] Ashish Bajel,[2,5] Catriona L. Halliday,[6,7] Orly Lavee,[8]

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



J.Fungi **2023, 9, 131. https://doi.org/**10.3390/jof9020131

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,

- Önceden başarılı olarak tedavi edilmiş İA öyküsü

+

- Takip eden bir immunosupresyon riski
  - Allojeneik HSCT (erken faz), otolog HSCT
  - Ağır nötropeniye yol açacak kemoterapi
    - (< 500/Ml ve en az 7 gün sürecek)
  - Yoğun kronik GVHD
- T hücre supresyon tedavisi (steroid)
- Tüm immunsupresyon periyodu boyunca

Intervention	SoR	QoE	Comment
Secondary prophylaxis with an *Aspergillus* active antifungal proven to be effective in the actual patient	A	II	Results compared to historical data, mostly in allogeneic HSCT setting
Voriconazole	A	II_h	IA: 31/45 patients, 1 year cumulative incidence of IFD 6.7 ± 3.6%, TDM
Caspofungin 70 mg day 1, followed by 50 mg/day IV until stable engraftment, followed by 400 mg itraconazole suspension PO	B	II_h	
L-AmB followed by voriconazole	C	II	Fungal infection related mortality 28% despite lipid-based AmB
Surgical resection following by secondary prophylaxis	B	III	Timing and methods of surgery important. Concomitant administration of appropriate antifungal compound justified Indication for surgical intervention by appropriate specialist. Interdisciplinary consensus needed

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,

Clinical Microbiology and Infection 24 (2018) e1–e38

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

Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Shahid Husain[1] | Jose F. Camargo[2] on behalf of the AST Infectious Diseases Community of Practice

TABLE 2 Antifungal therapy for IA in adult organ transplant recipients

Drug	Dosing (adult)	TDM	Comments
Primary therapy			
Voriconazole	6 mg/kg IV/PO[a] every 12 h for 1 d, followed by 4 mg/kg IV/PO every 12 h	Target trough level for treatment is >1 mg/L.[179,180,184] A level of 1-5.5 mg/L is considered adequate for most patients. A higher target (eg, 2-6 mg/L) should be used if there is disease with a poor prognosis (eg, CNS infection, bulky disease, multifocal infection); infections with pathogen with elevated MICs (eg, an MIC of 2 mg/L)[128]	Due to accumulation of the IV vehicle (cyclodextrin), the manufacturer recommends the use of oral voriconazole in patients with CrCl <50 mL/min. In clinical practice, however, IV voriconazole has been safely administered to patients with different degrees of renal failure[209,210]
		Once steady-state levels have been reached, repeat sampling is warranted every 3-5 d[184] in unstable patients and when there is uncertainty about voriconazole concentrations	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended
		Measurement of serum trough concentration within 5-7 d	Non-linear (ie, highly variable) pharmacokinetics

Clinical Transplantation. 2019;33:e13544.

Alternative therapies			
Isavuconazole	372 mg (isavuconazole 200 mg) IV/PO[a] every 8 h for 6 doses, followed by 372 mg (isavuconazole 200 mg) IV/PO once daily	Trough level in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 suggests adequate drug exposure[128] No apparent relationship between exposure and efficacy to support routine TDM for isavuconazole[183] Has 130-h half-life—long clearance after discontinuation	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended Dose adjustment is not required in renal impairment Linear pharmacokinetics with low interpatient variability[136]
Liposomal amphotericin B (AmBisome®)	3-5 mg/kg/d IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, and renal and hepatic function is recommended Higher dosages are not more effective Better tolerated than Abelcet®
Amphotericin B Lipid Complex (Abelcet®)	5 mg/kg/d IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, and renal and hepatic function is recommended Higher dosages are not more effective
Other therapies[b]			
Anidulafungin	200 mg IV on day 1 and 100 mg IV daily thereafter	There is currently insufficient evidence to support the routine use of TDM	It has been evaluated only as salvage therapy. Its role as single-agent therapy is controversial It does not require dosage adjustments in patients with renal or hepatic dysfunction
Caspofungin	70 mg IV on day 1 and 50 mg IV/d thereafter	There is currently insufficient evidence to support the routine use of TDM	It has been evaluated only as salvage therapy. Its role as single-agent therapy is controversial. Monitoring of hepatic function is recommended Dose adjustment is not required in renal impairment Drug interactions are less clinically important
Micafungin	100-150 mg IV daily	There is currently insufficient evidence to support the routine use of TDM	Monitoring of hepatic function is recommended Non-FDA-approved use (for treatment of IA) Dose adjustment is not required in renal impairment Drug interactions are less clinically important

Drug	Dosing (adult)	TDM	Comments
Posaconazole	300 mg PO (delayed-release tablets)}/IV twice daily on day 1 followed by 300 mg PO (delayed-release tablets)}/IV once daily on day 2 and thereafter	Target trough level for treatment is >1 mg/L[184] (preferably >1.25 mg/L)	Although the delayed-release tablet can be taken without food, a high-fat meal (~70 g fat) can increase its serum concentration by ~1.5-fold[295]
	When using suspension 200 mg PO every 8 h or 400 mg PO every 12 h	Measurement of serum trough concentration within 7 d of initiation of therapy or following dose adjustment[184]	Dose adjustment is not required in renal impairment. Dose after HD in patients on RRT Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended Non-FDA-approved use (for treatment of IA)
Itraconazole	200 mg PO 3 times daily for the first 3 d of therapy, followed by 200-400 PO mg/d	Target trough level is >0.5-1 mg/L[178] ^{3}Hydroxy-itraconazole is an active metabolite with antifungal activity similar to itraconazole. Assays that measure total (itraconazole + hydroxy-itraconazole) concentration of itraconazole are preferred	Itraconazole capsules are poorly orally bioavailable, and absorption is both food- and acid-dependent. In contrast, the oral solution has better bioavailability and there is no significant food or acid effect
		Measurement of serum trough concentration within 5-7 d	Use with caution in patients with renal impairment; some recommend decreasing dose by 50% in CrCl <10 mL/min Use should be considered only in mild cases intolerant to other therapies

Clinical Transplantation. 2019;33:e13544.

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

Philipp Koehler, Matteo Bassetti, Arunaloke Chakrabarti, Sharon C A Chen, Arnaldo Lopes Colombo, Martin Hoenigl, Nikolay Klimko,

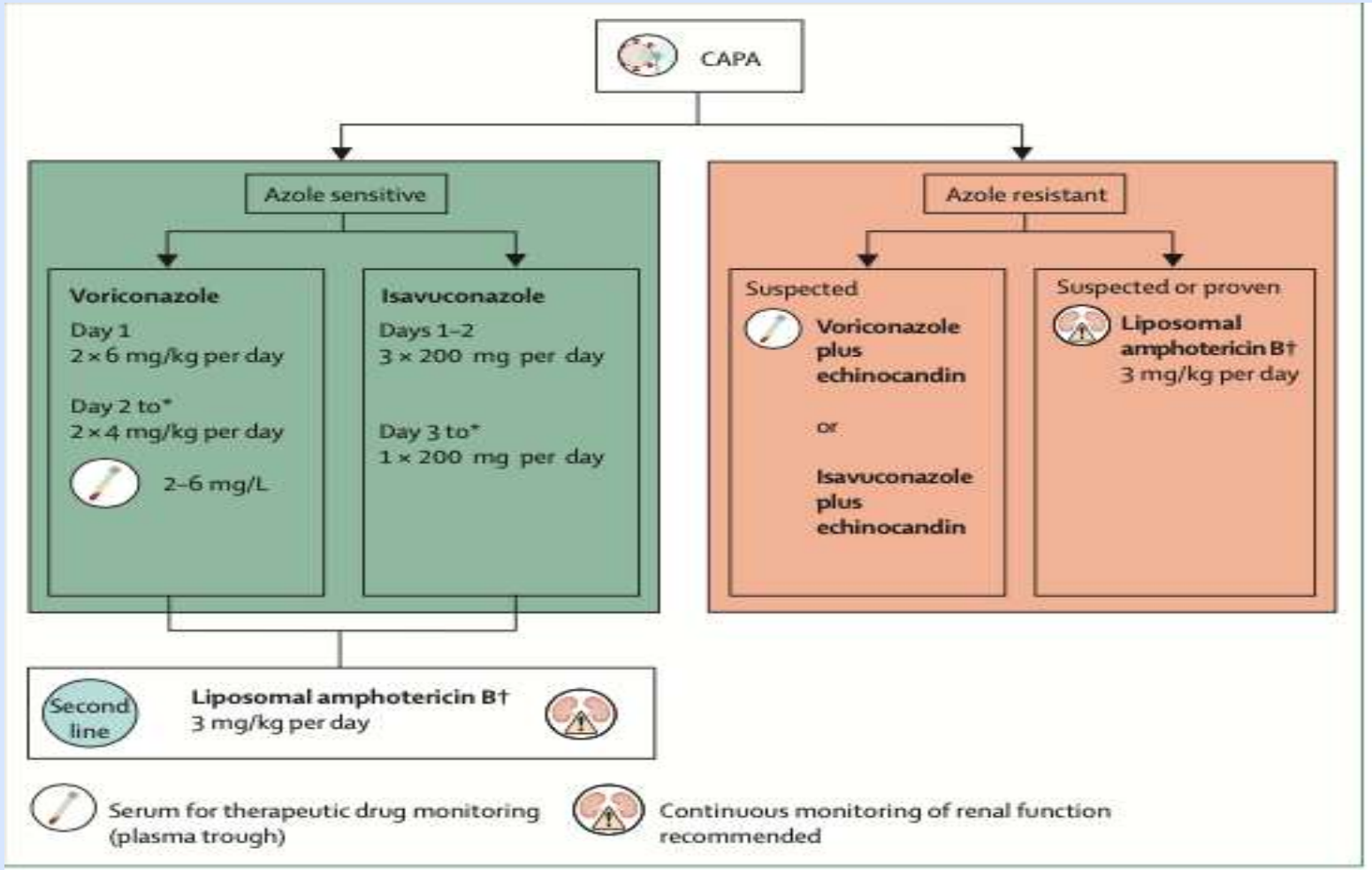


Figure 3: **Recommended treatment for CAPA**

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],

Table 2. Monoclonal antibody-mediated therapeutic effects in *Aspergillus* infection.

Therapeutic Effects	MAb	Subclass	References
Fungal growth inhibition/fungicidal activity (in vitro)	C7, K10, A9, Mab-7, SMB19, R-5, MS112-IIB1, YW327.6S2, 3G11 and 5H5	IgM, IgG, IgG1, IgG3	[110,112,113,115,120–124]
Fungal growth inhibition/fungicidal activity (in vivo)	K10, A9, 2G8, R-5, 3G11 and 5H5	IgM, IgG1, IgG2b, IgG3	[112,115,118,123,125,126]
Germination suppression (in vitro)	K10, A9, 2G8, R-5, 3G11 and 5H5	IgM, IgG1, IgG2b, IgG3	[112,115,118,123,125,126]
Attachment inhibition (in vitro)	2G8, Mab-7, AK-14	IgG2b, IgM	[109–111,125]
Protease inhibition (in vivo)	BB11, MB8, KD5, GD11, and CCIII 19	IgG1 and IgG2a	[119]
Immunological enhancement (in vitro and in vivo)	A9, SMB19, MS112-IIB1, 3G11, 5H5, YW327.6S2	IgG1, IgM, IgG1, IgG3, IgG	[112,113,122–124]
Drug mediator (in vitro and in vivo)	MPS5.44	IgM	[127]

Ekstrapulmoner Aspergilloz Tedavi Yaklaşımları

Table 9 Extrapulmonary aspergillosis management recommendations

Condition	Recommendation	Comments	SoR	QoE
CNS aspergillosis	Systemic voriconazole therapy		A	II
	Surgical resection of focal CNS lesions	Particularly if poor response to medical therapy	B	II
Acute invasive *Aspergillus* sinusitis	Urgent ENT review and surgical debridement		A	II
	Empiric liposomal amphotericin B therapy		A	II
	Systemic voriconazole therapy		A	II
Aspergillus endophthalmitis	Early vitrectomy		A	II
	Intravitreal voriconazole		A	III
	Systemic voriconazole therapy		A	III
Aspergillus keratitis	Topical natamycin		A	I
	Systemic voriconazole therapy	Not recommended based on RCT data	D	I
Aspergillus osteomyelitis	Systemic voriconazole therapy		A	II
	Surgical debridement		A	II

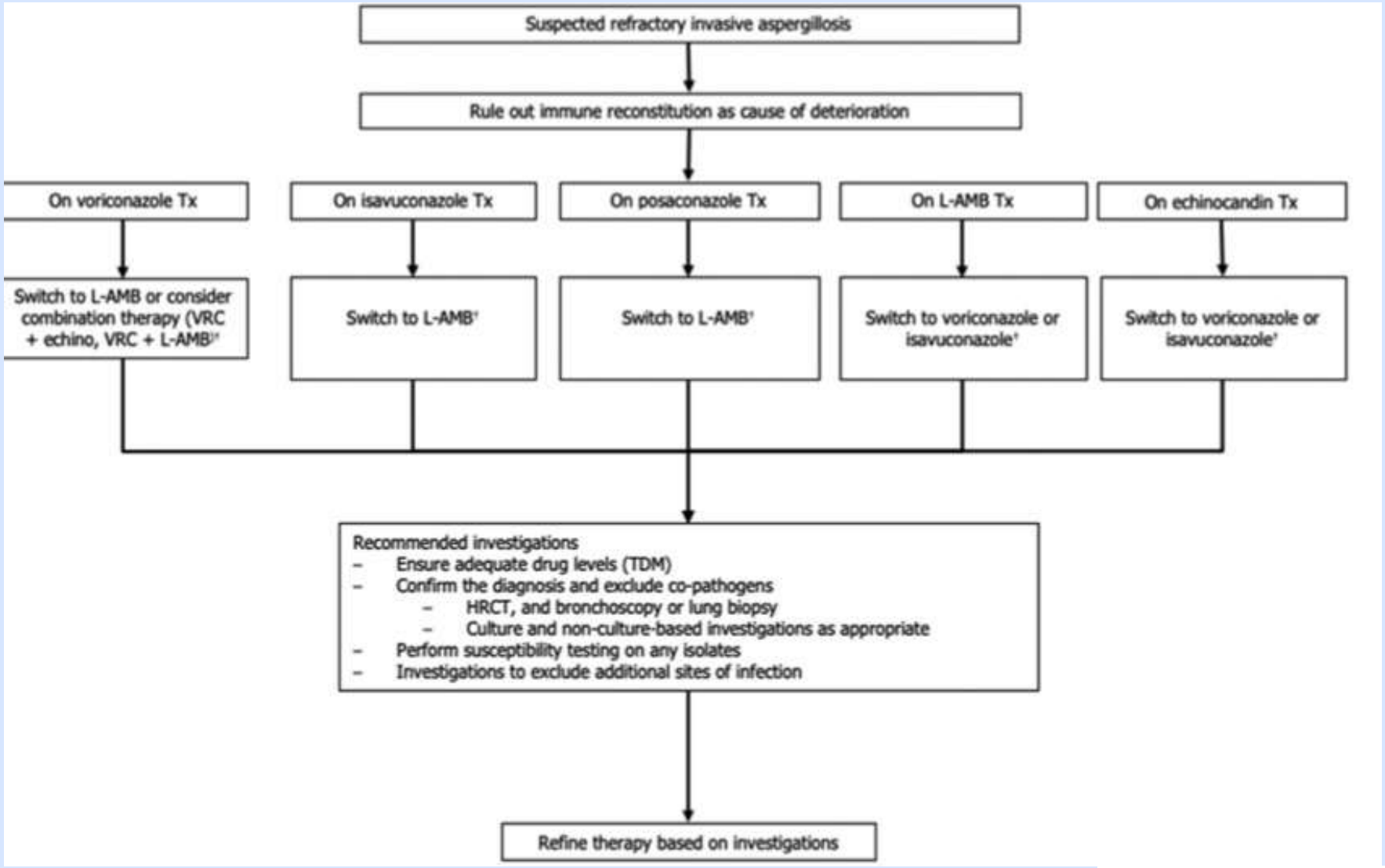
Internal Medicine Journal (2021) 51(Suppl. 7) 143–176

Tedavi süresi

- Optimal tedavi süresi
  - Altta yatan hastalık
  - Bağışıklık durumu
  - Tedaviye yanıt
- Tüm klinik ve radyografik anormalliklerde düzelme
- *Aspergillus* kanıtının olmaması
  - Mantar biyobelirteçleri ve kültürler
  - En az 6-12 hafta

Clinical Infectious Diseases 2016;63(4):e1–60
Clinical Transplantation. 2019;33:e13544.

Dirençli invaziv aspergilloz tedavisine yaklaşım

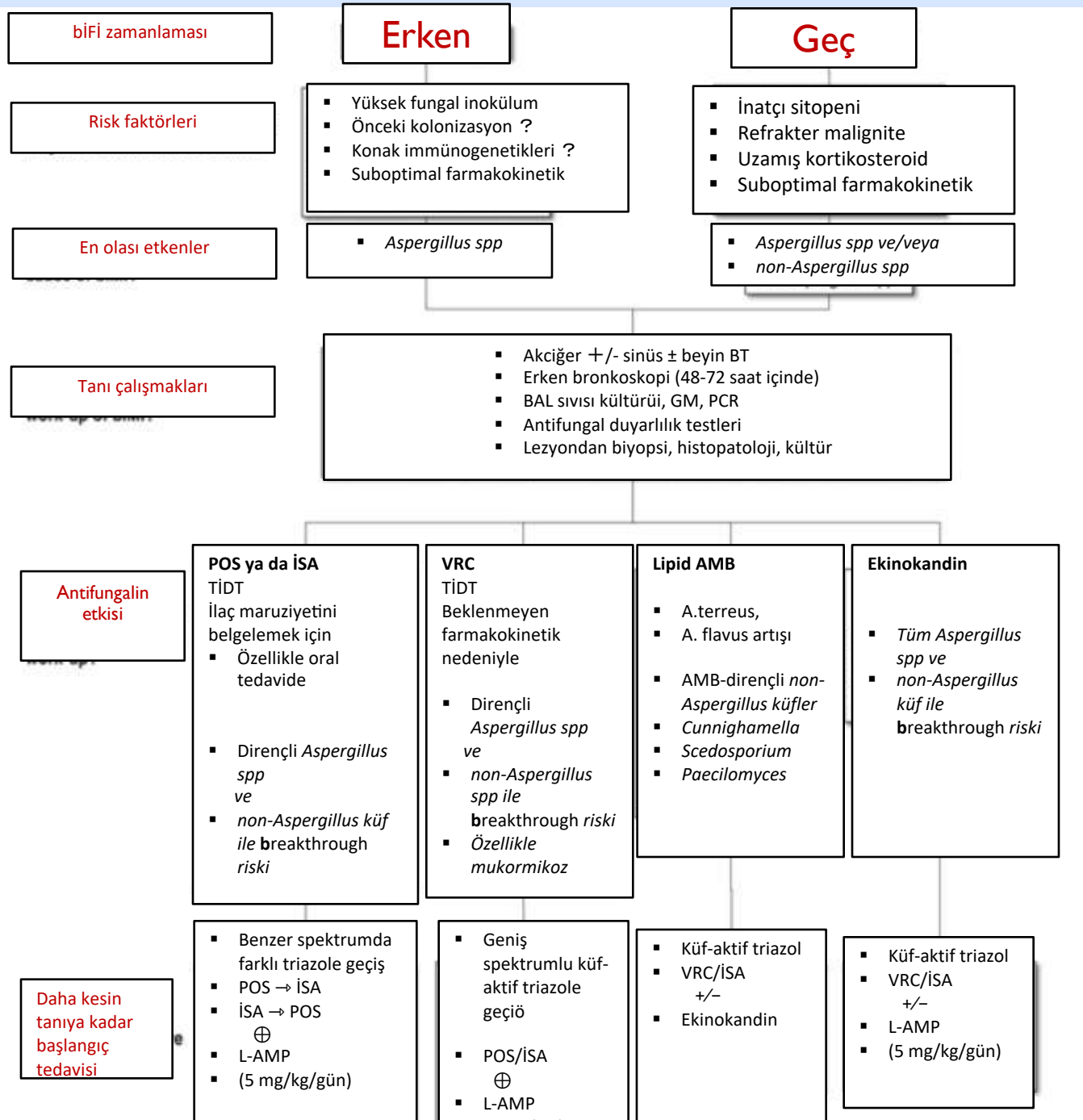


Internal Medicine Journal (2021) 51(Suppl. 7) 143–176

“Breakthrough” İFİ (bİFİ)

- İFİ önlemek için antifungal profilaksi uygulamaları
  - İFİ’de azalma
  - Epidemiyolojide değişiklik
  - bİFİ gelişimi
    - Yüksek morbidite ve mortalite
    - Tanı güç
      - Küf-aktif profilaksi ile biyobelirteçlerin performansında azalma

Lionakis MS. CID 2018;67(10):1621–30.
Cornely OA. Mycoses 2019;62:716–729.
Jenks JD. Mycoses 2020;63:1021–1032.



Lionakis MS. CID 2018;67(10):1621–30.

Azol Dirençli Suşlar İçin Yeni Sınıf İlaçlar

Drug	Class	Mechanism of Action	Route of Administration
Foxmanogepix	Gwt1 inhibitor	Inhibit mannoprotein maturation and impair fungal cell wall integrity	Oral
Ibrexafungerp	Triterpenoid	Inhibit β-D glucan synthesis and impair fungal cell wall integrity	Oral
Olorofim	Dihydroorotate dehydrogenase inhibitor	Inhibit pyrimidine synthesis	Oral
Opelconazole	Triazole	Lanosterol 14α-demethylase inhibition	Nebulized

Diagnostics 2022, 12, 2712. https://doi.org/10.3390