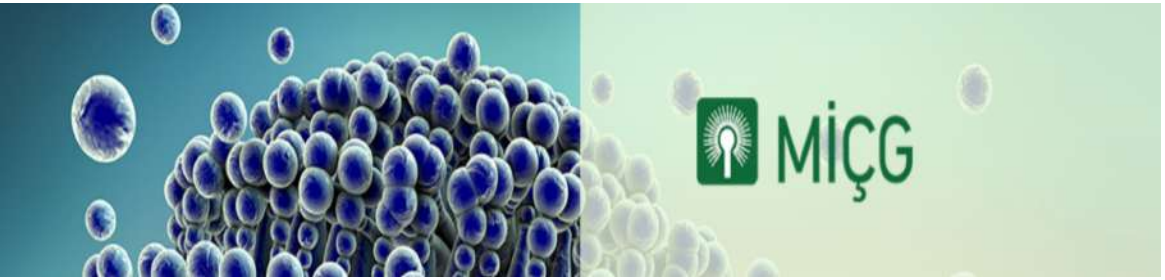
KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

İnvaziv Aspergillozda Tanı

Yasemin TEZER



T.C. SAĞLIK BAKANLIĞI ANKARA BİLKENT ŞEHİR HASTANESİ

TÜRKİYE YÜKSEK İHTİSAS HASTANESİ 1964 ANKARA

Sunumda

- Biraz sayılar
- İnvazif Aspergilloz tanımı
- İnvaziv Aspergilozda tanıda **soru(sorun)**
- Akademik tanımlamalar
- Kliniğe uygulanması

İnvaziv Fungal İnfeksiyon

- Dünyada yaklaşık **3 milyon** insan **kronik ciddi fungal** infeksiyon ile,
- Bunların **yılda 1.9 milyonu İFİ**
- Çoğu hayatı tehdit eden infeksiyonlar, **yılda yaklaşık 1.6 milyon mortalite** ile ilişkili olduğu tahmin edilmekte.
- Morbidite ve mortalite yanı sıra **ciddi ekonomik yük**
- ABD'de **sadece hospitalizasyonların** değerlendirildiği fungal infeksiyonların **maliyeti 4.6 milyon** dolar; **1.2 milyon doları Aspergillus** inf ile ilişkili (*fungal dx öncesi gereksiz tahlil , ampirik başlanan Ab ve gereksiz medikal müdahaleler dahil değil*)
- **Premortem İFİ tanısı yaklaşık %50** (%12-60 etiyoloji ve altta yatan hastalıklara göre değişken)

İnvaziv Pulmoner Aspergilloz

- **Mortalite %90'ların üzerinde**, tanısal güçlük…

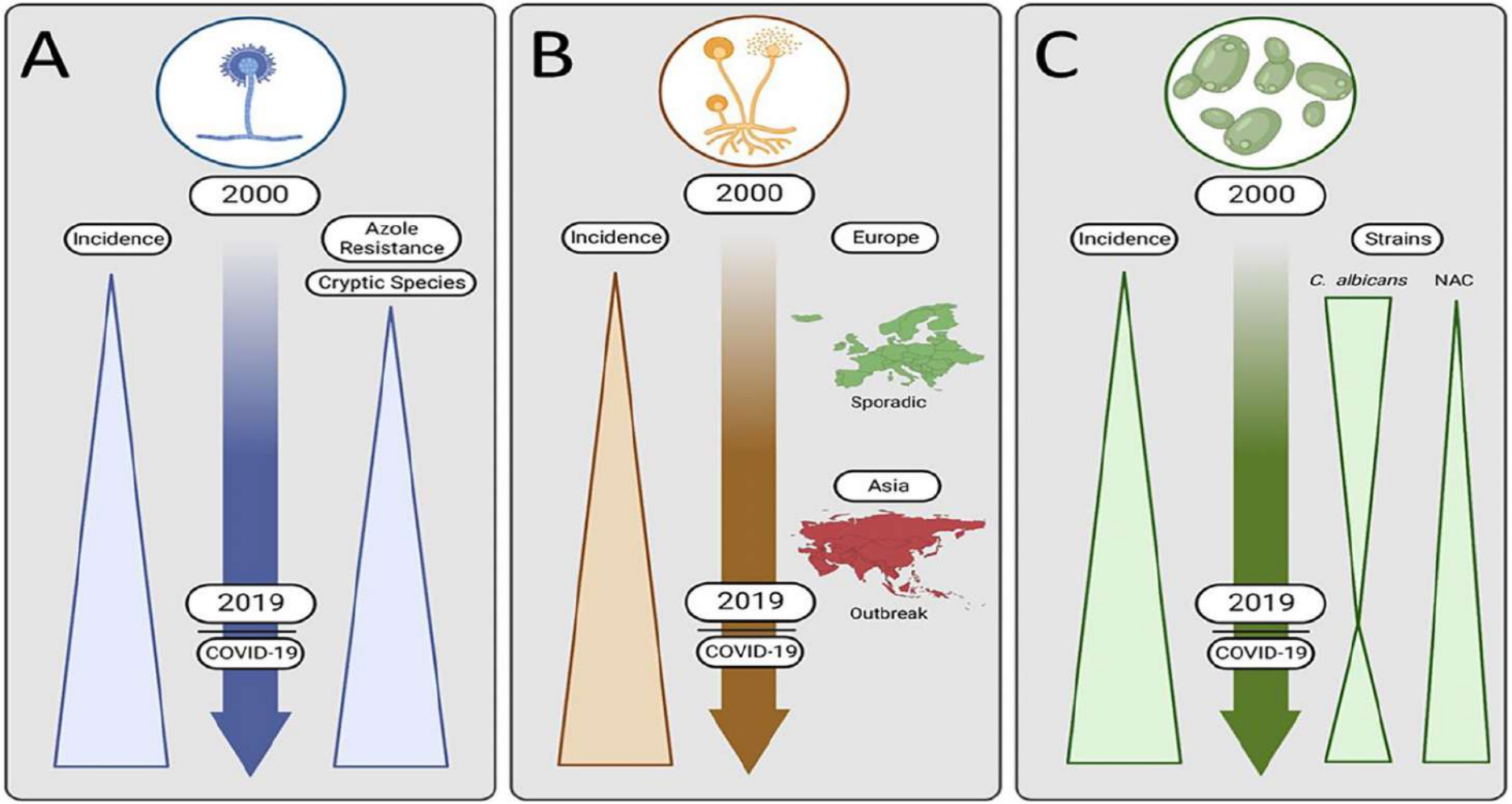
- 25 yıl süren **(1991-2016)** postmortem çalışmada, 25 hastaya **(%2,8)** otopside IPA teşhisi konuldu ve bunlardan yalnızca 10'u (%40) antifungal tedavinin başlatılmasına dayanarak IPA ante-mortem olarak sınıflandırılabildi.

- Bu postmortem tanıyla ilişkili **en yaygın komorbid durumlar kortikosteroid tedavisi (%56), KOAH (%44).**

APMIS 131: 654–667

Mercier *et al. Crit Care* *(2020) 24:642*

Fungal İnfeksiyonlarda Değişen Epidemiyoloji



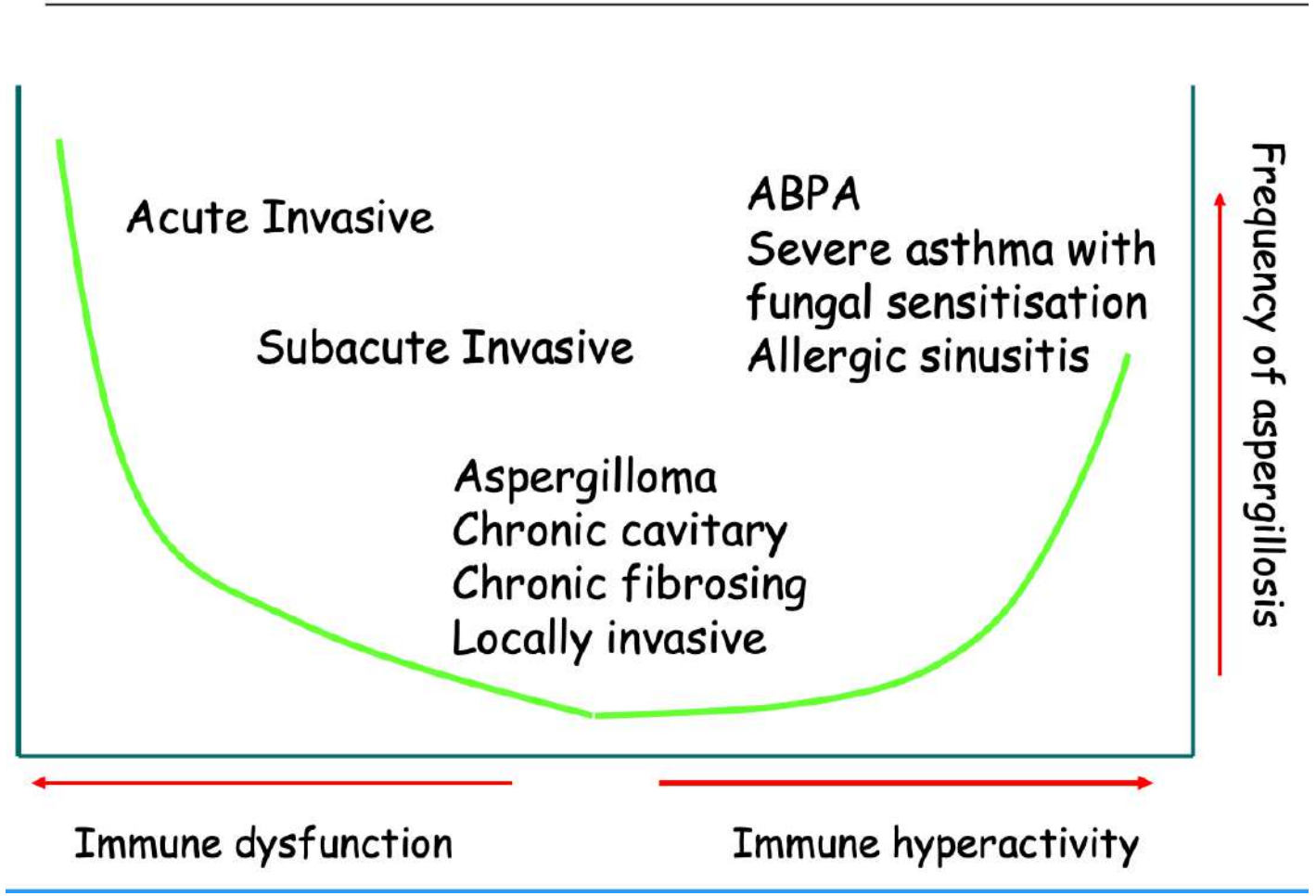
Molecular Aspects of Medicine 94 (2023) 101215

	Mean annual incidence (thousands)	Treated mortality (%)	Untreated mortality* (%)	Ratio of treated to untreated cases*	Mean estimated deaths (thousands)	Percentage of deaths attributable to fungal infection (%)	Attributable deaths (thousands)
Invasive aspergillosis in COPD	1513 (753–2272)	43–72%	>95%	1:5	1325	~80%	1060
Invasive aspergillosis in ICU	519 (208–1038)	50% (46–82)	>95%	1:3	416	~50%	208
Invasive aspergillosis in leukaemia and lymphoma, and allogeneic HSCT	27	45% (30–57)	>95%	10:1	14	~80%	11
Invasive aspergillosis (lung cancer)	57*	51%	>95%	1:4	49*	~40%	19*
Chronic pulmonary aspergillosis	1837	8%	20%	1:12	340*	60% (0–85·7)	204*

(İA insidansı ve mortalitesine ilişkin mevcut tahminler kesin değildir. Risk altındaki nüfus paydaları, 2019-21 için yıllık insidansı tahmin etmek için kullanılmıştır. 2010'dan 2023'e kadar yapılan kapsamlı literatür taramaları, bireysel ülke ve küresel hastalık yüküne ilişkin 85'ten fazla makale. 120'den fazla ülkeden elde edilen veriler dahil edilmiştir.)

Kaba ve atfedilebilir mortalite, **tedavi edilmemiş mortalite**,
Farkındalık, kılavuzlar ve **teşhis ve tedavilerin erişilebilirliği**, tedavi edilen vakaların tedavi edilmeyen vakalara oranını belirliyor!!!!
Tahminler influenza veya COVID-19 salgınlarını içermemektedir.
Her yıl 2.113.000'den fazla kişide kronik obstrüktif akciğer hastalığı, yoğun bakım, akciğer kanseri veya hematolojik malignite bağlamında invazif aspergilloz gelişmekte ve **yıllık kaba mortalite** 1.801.000'dir **(%85-2).**

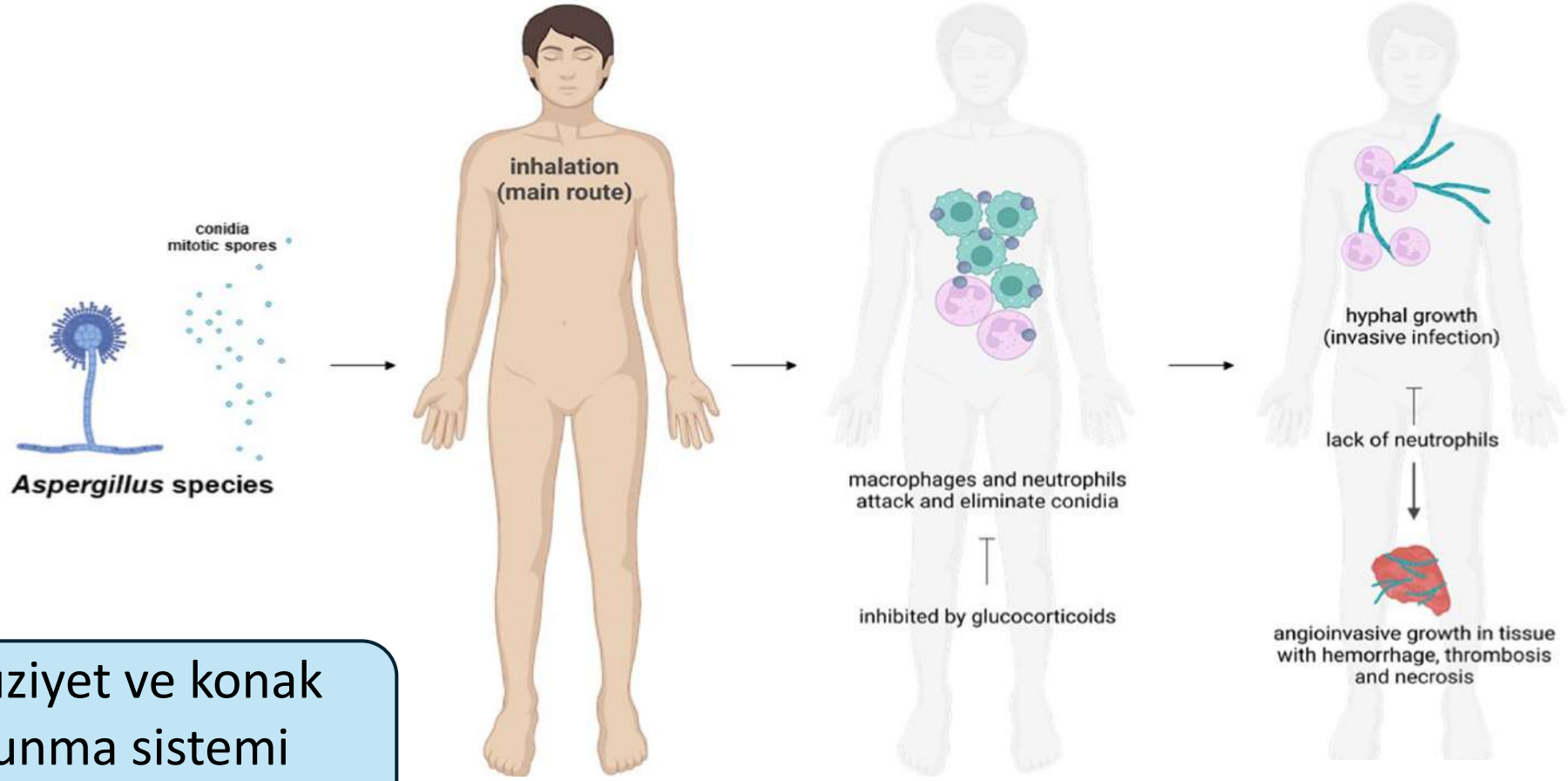
Lancet Infect Dis 2024; 24: e428–38



Aspergilloz spektrumu konak faktörlerine ve immün cevaba göre değişir.

Aspergilloz patogenez

%10-25 hastada dissemine

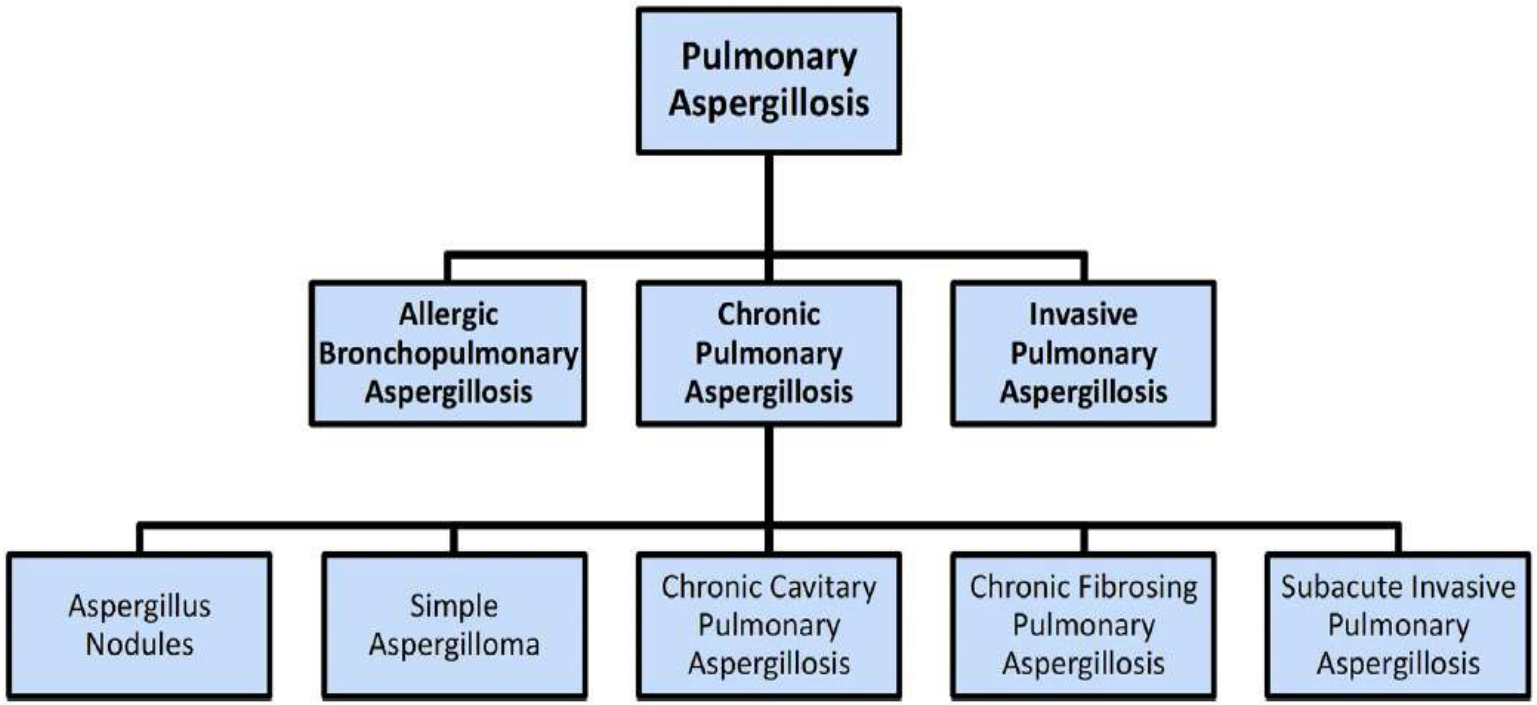


Maruziyet ve konak savunma sistemi arasındaki denge

Molecular Aspects of Medicine 94 (2023) 101215

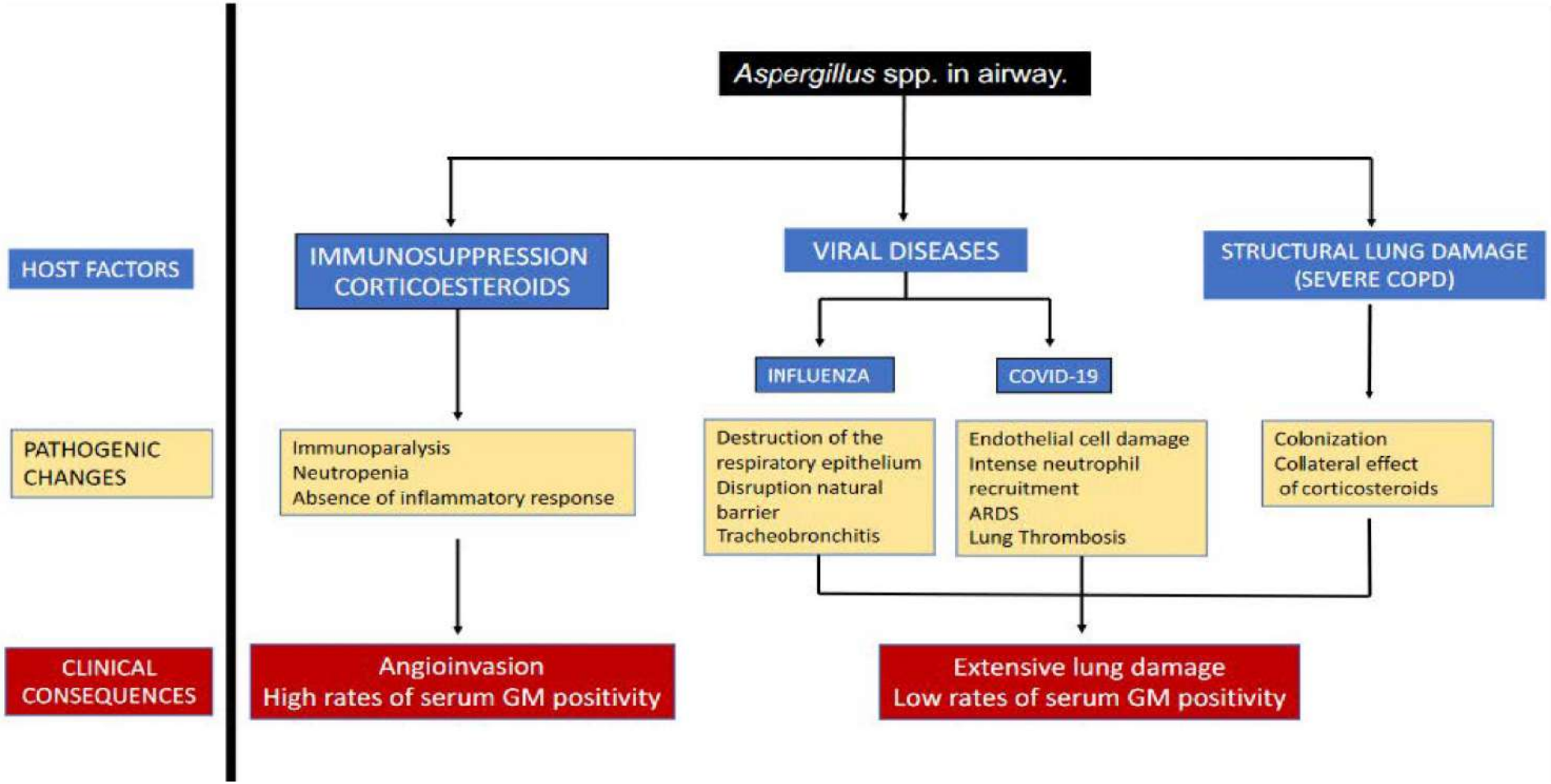
Respiratory Medicine 141 (2018) 121–131

Aspergilloz Klinik Spektrumu



Respiratory Medicine 141 (2018) 121–131

Patofizyolojiye Göre Klinik Sonlanım



Diagnostics 2023, 13, 440

İnvaziv Aspergilloz

- İnvaziv pulmoner aspergilloz
- Trakeobronkial aspergilloz
- Ekstrapulmoner aspergilloz

(Sinus, oküler, osteomiyelit, SSS…)

Infect Dis Clin North Am. 2021 Jun;35(2):415-434.

Respiratory Medicine 141 (2018) 121–131

İnvaziv Aspergillozda Tanı

Risk faktörlerine göre, **(şüphe eşiği düşük, araştırma eşiği yüksek)**

- Histopatolojik
- Mikrobiyolojik
- Seroloji
- Görüntüleme

Test	Microscopy Histology	Culture	Biomarkers	Molecular
Time	10 min-3-7 days	3-28 days	1-3 h	5-72 h
Pros	✓ Fast ✓ Invasion	✓ Specific ✓ Epidemiology ✓ AFST	✓ Fast ✓ Invasion ✓ POC available	✓ Fast ✓ Invasion
Cons	❖ Sensitivity ❖ Expertise	❖ Slow ❖ Sensitivity	❖ Specificity ❖ Availability	❖ Complex ❖ Non sterile samples?

İA için risk faktörleri

YBÜ hastaları

High risk	Intermediate risk	Low risk
• Neutropenia (<500 neutrophils/ mm^3)	• Prolonged treatment with corticosteroids	• Severe burns
• Haematolog		s (*e.g.*
(risk is high		ients)
• Allogenic b		ys
transplantat		
	• Solid-organ cancer	• Post-cardiac surgery status
	• HIV infection (risk increases with lower CD4 count)	
	• Lung transplantation	
	• Systemic diseases requiring immunosup-pressive therapy	

DEĞİŞEN İKLİM ve ÇEVRESEL FAKTÖRLER…

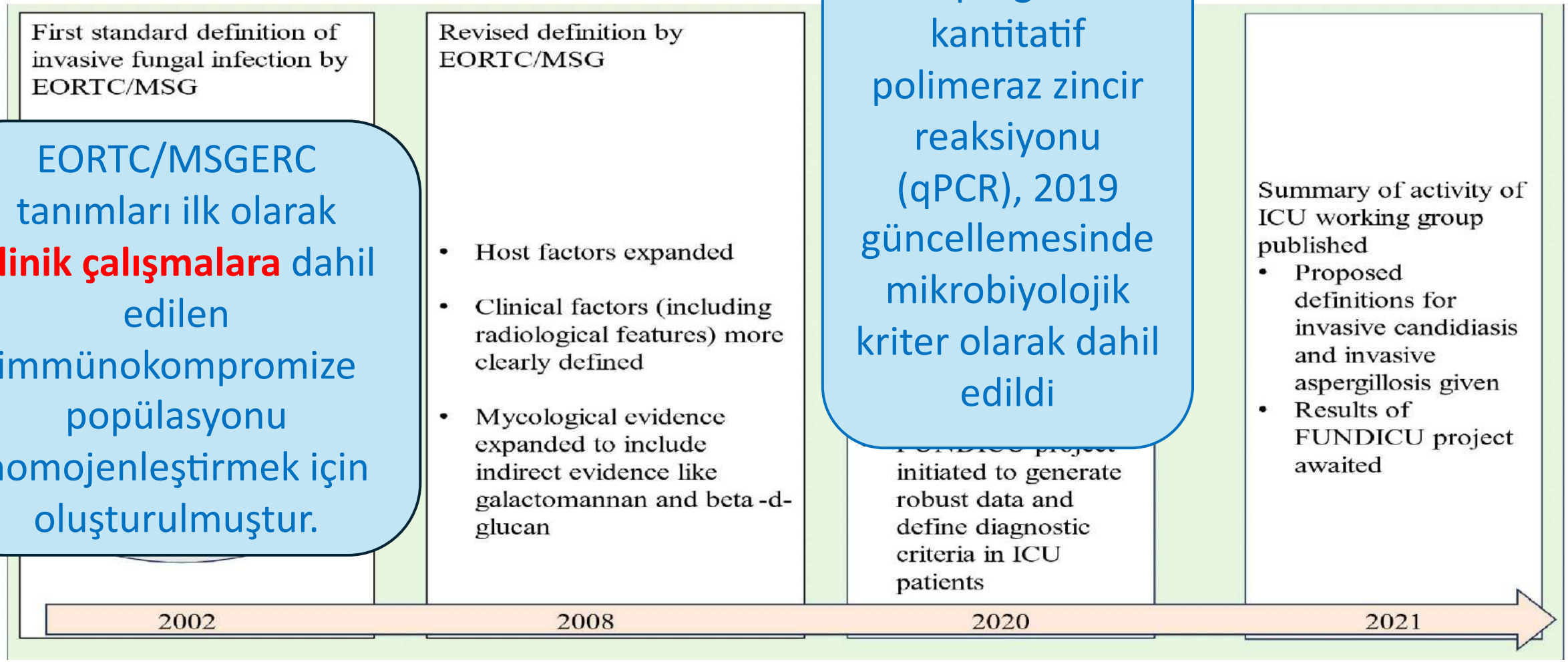
İbrutinib dissemine inf nedeni, yeni imm.modülatör ve imm. süpresif ajanlar İPA artış

Viral solunum yolu infeksiyon etkenleri (İnfluenza, SARS-CoV2, RSV..)

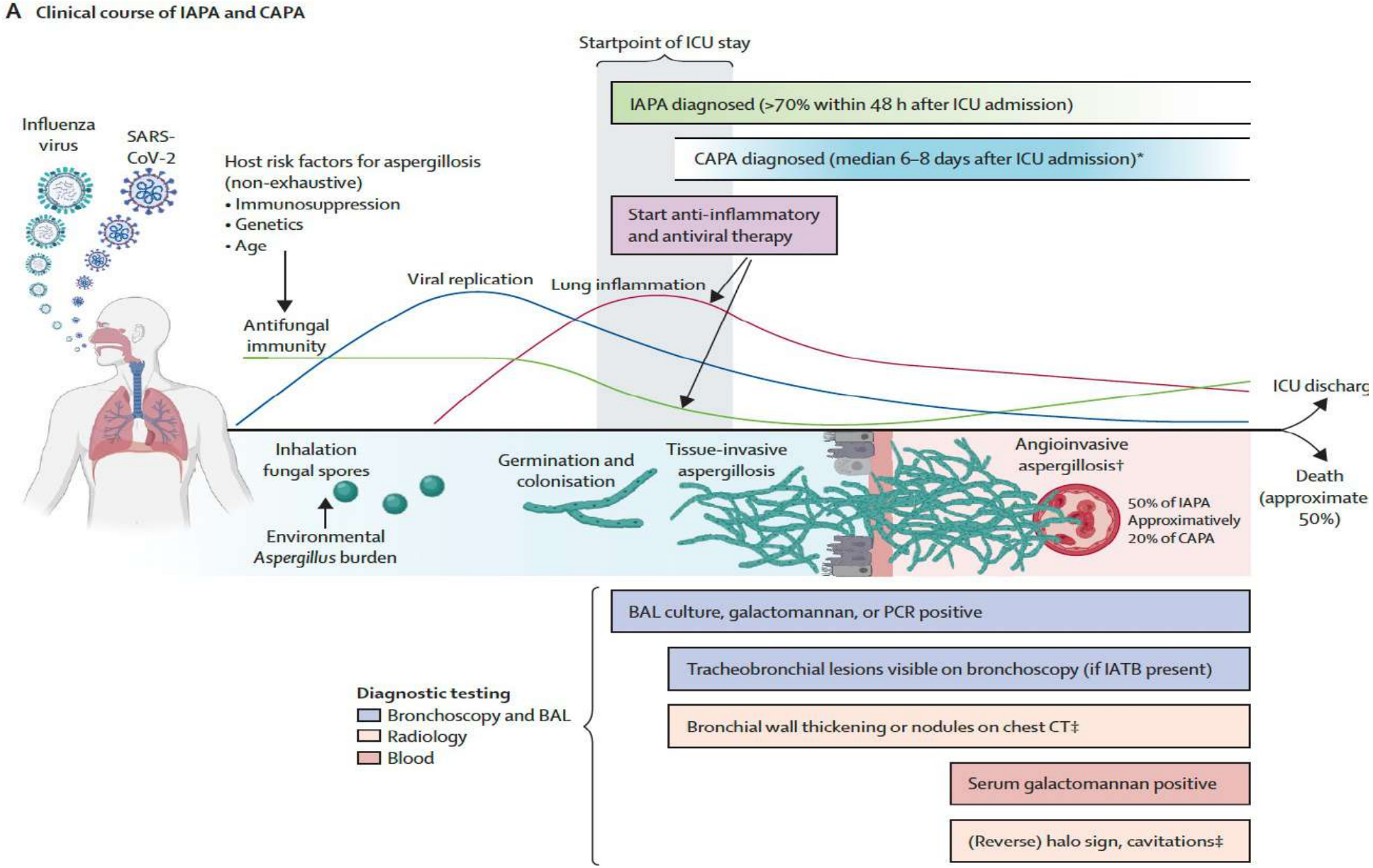
İnvaziv Fungal İnfeksiyonlar Tanımının Tarihsel Gelisimi

EORTC/MSGERC tanımları ilk olarak **klinik çalışmalara** dahil edilen immünokompromize popülasyonu homojenleştirmek için oluşturulmuştur.

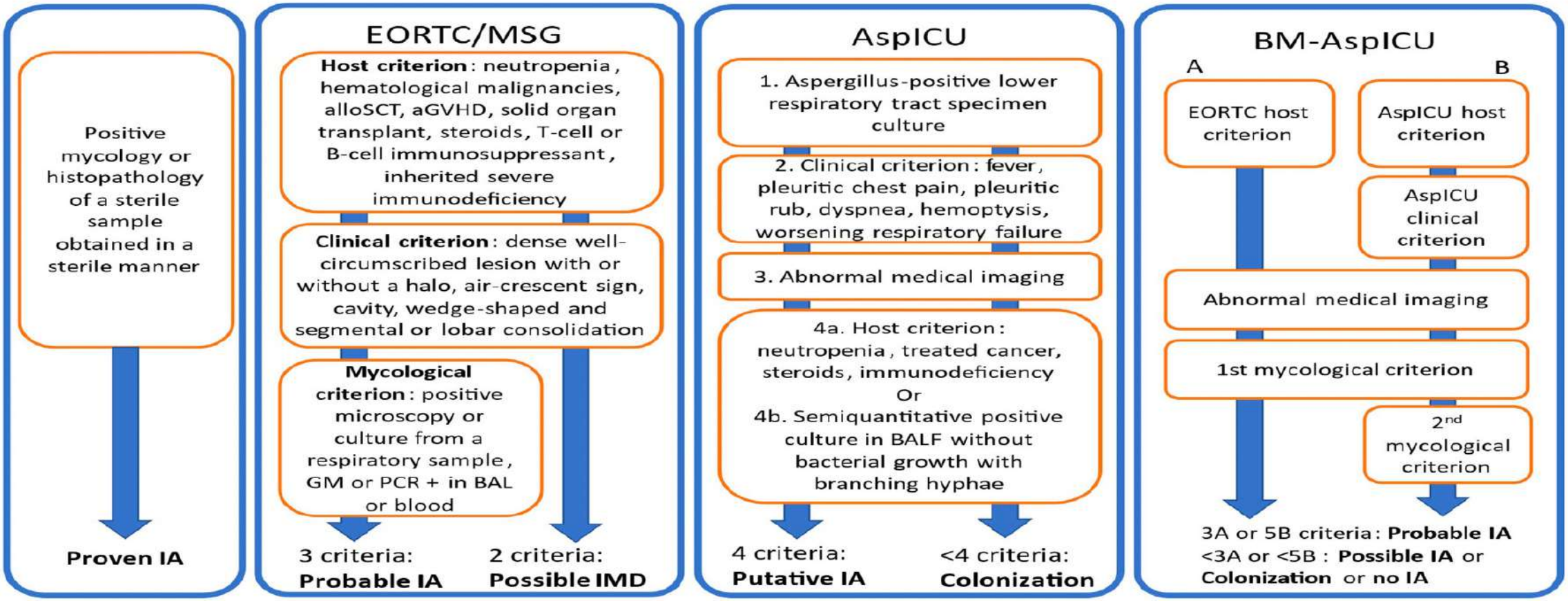
Aspergillus kantitatif polimeraz zincir reaksiyonu (qPCR), 2019 güncellemesinde mikrobiyolojik kriter olarak dahil edildi



Front. Cell. Infect. Microbiol. 14:1256158.
doi: 10.3389/fcimb.2024.1256158


A Clinical course of IAPA and CAPA
Startpoint of ICU stay
IAPA diagnosed (>70% within 48 h after ICU admission)
CAPA diagnosed (median 6–8 days after ICU admission)*
Start anti-inflammatory and antiviral therapy
Influenza virus
SARS-CoV-2
Host risk factors for aspergillosis (non-exhaustive)
• Immunosuppression
• Genetics
• Age
Antifungal immunity
Viral replication
Lung inflammation
ICU discharg
Death (approximate 50%)
Inhalation fungal spores
Environmental Aspergillus burden
Germination and colonisation
Tissue-invasive aspergillosis
Angioinvasive aspergillosis†
50% of IAPA
Approximatively 20% of CAPA
Diagnostic testing
Bronchoscopy and BAL
Radiology
Blood
BAL culture, galactomannan, or PCR positive
Tracheobronchial lesions visible on bronchoscopy (if IATB present)
Bronchial wall thickening or nodules on chest CT‡
Serum galactomannan positive
(Reverse) halo sign, cavitations‡

Son EORTC güncellemesine kadar …



J. Fungi **2023**, *9*, 131

Tanımlamalar…

Disease definitions based on clinical, host and mycological criteria

Disease-definitions: probable pulmonary aspergillosis	Important factors: Host	Important factors: Clinical	Mycological criteria (at least one of the following criteria must be positive)
Probable pulmonary aspergillosis (EORTC/MSG)	(1) (2) (3) (4)	A or B	Microscopy: fungal hyphae in sputum, bronchoalveolar lavage (BAL), bronchial brush, or aspirates indicating *Aspergillus* Culture: *Aspergillus* sp. of BAL or bronchial secretions Biomarker: single serum or plasma GM ≥1.0, BAL GM ≥1.0, single serum or plasma GM ≥0.7 and BAL GM ≥0.8, cerebrospinal fluid ≥1.0 *Aspergillus* PCR (2 ≥ consecutive positive PCRs on plasma, serum, or whole blood; or 2 ≥ positive PCRs on BALs)
Putative invasive pulmonary aspergillosis in critically ill patients	(1) (2) (3) (5) (6)	C + D + E	Positive *Aspergillus*-culture from lower respiratory tract and semi-quantitative culture of BAL without bacterial growth, together with a positive cytological smear showing branching hyphae
Influenza-associated pulmonary *aspergillosis (IAPA)*	(7)	B or F	Serum GM >0.5, BAL GM ≥1.0, positive BAL or sputum culture (tracheobronchitis); hyphae via microscopy consistent with *Aspergillus* sp.
Covid-associated pulmonary *aspergillosis* (CAPA)	(8)	B or F	Microscopy: fungal hyphae in BAL consistent with *Aspergillus* sp.; positive BAL culture or PCR; Serum GM >0.5 or serum LFA >0.5; BAL GM ≥1.0 or BAL LFA index ≥1.0 ≥2 consecutive positive *Aspergillus* PCR in plasma, serum, or whole blood; a single positive *Aspergillus* PCR in BAL (<36 cycles); single positive *Aspergillus* PCR in plasma, serum, or whole blood, and a single positive in BAL (any threshold cycle permitted)

Abbreviations: EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycosis Study Group; GM, galactomannan; LFA, Lateral flow device

Host criteria

(1) Neutropenia (> 10 days EORTC)
(2) Prolonged corticosteroide use > 0.3 mg/kg ≥ 3 weeks (EORTC)
(3) Hematological malignancy
(4) Receipt of allogeneic stem-cell transplant or solid organ transplant, treatment with T-cell immunosuppressants, B-cell receptor pathways, BCL2 inhibitors, inherited severe immunodeficiency, acute graft-versus-host disease (grade III/IV)
(5) Oncological malignancy and cytotoxic agents
(6) Acquired immunodeficiency
(7) Influenza-like illness
(8) COVID-19 diseases

Clinical criteria

A Pulmonary aspergillosis CT: dense, well-circumscribed lesion +/- halo sign, air crescent, cavity, wedge-shaped and segmental or lobular consolidation
B Tracheobronchitis: ulceration, nodules, pseudomembranes, plaque, or eschar
C Refractory and fever despite antibiotics (48 h)
D Pleuritic chest pain, pleuritic rub, dyspnoe, hemoptosis, worsening respiratory insufficiency
E Abnormal medical imaging
F Pulmonary infiltrate or cavitary infiltrate

Clinical Microbiology and Infection 27 (2021) 1230–1241

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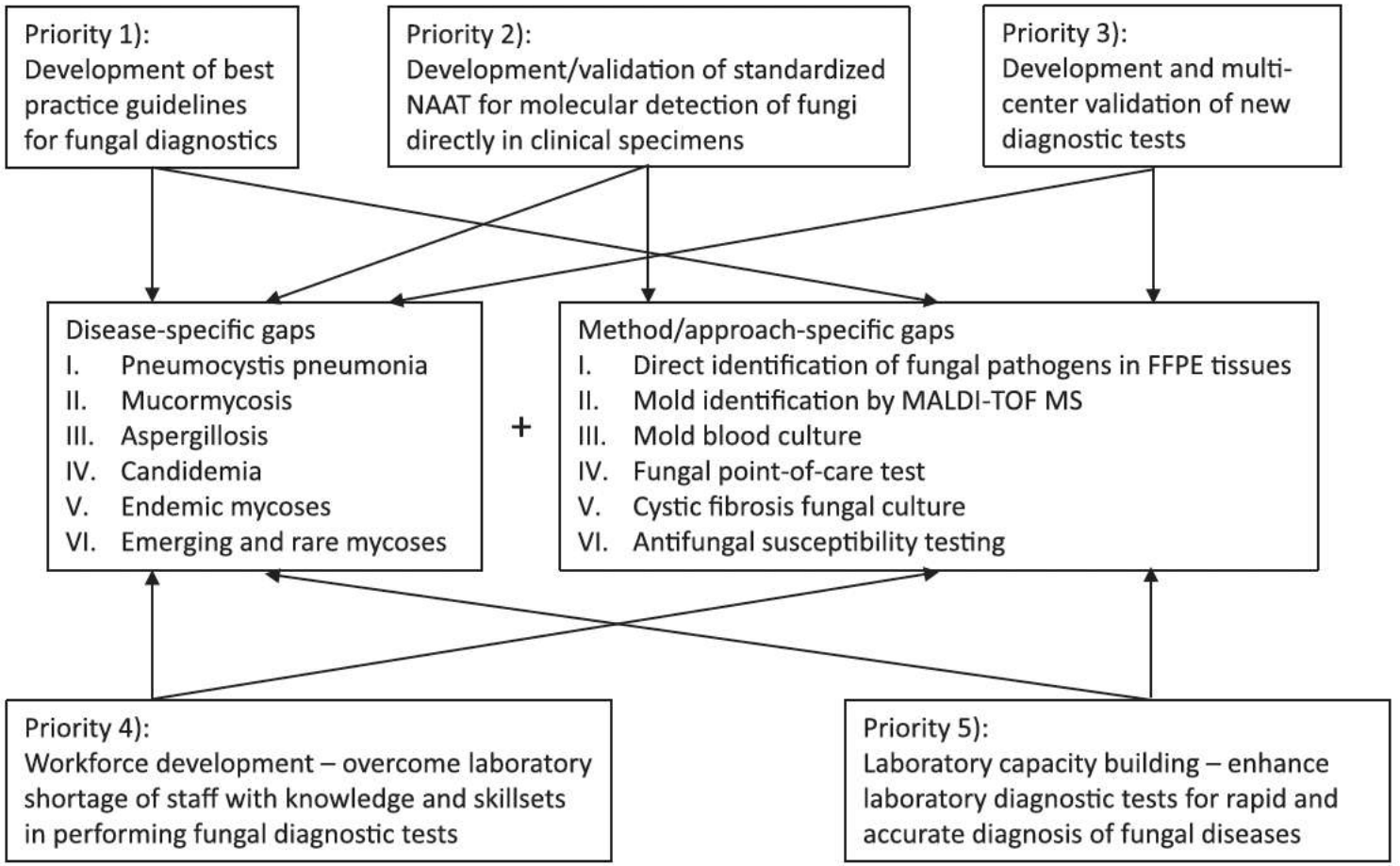
COMMENTARY

Recognition of Diagnostic Gaps for Laboratory Diagnosis of Fungal Diseases: Expert Opinion from the Fungal Diagnostics Laboratories Consortium (FDLC)



2021'de Fungal Diagnostics Laboratory Consortium, invaziv fungal enfeksiyonların teşhisinde hastalığa özgü ve metodolojiye özgü açıklıkları yayınladı

Table 1 Diagnostic criteria for invasive pulmonary aspergillosis
BM-AspICU

Criteria
Neutropenia (< 500 neutrophils/mm^3 for > 10 days)
Receipt of an allogenic stem cell transplant
Corticosteroids > 0.3 mg/kg/day for > 3 weeks
Treatment with recognized T-cell immunosuppressant for more than 90
Inherited severe deficiency
Underlying hematological or oncological malignancy treated with cyto
Ibrutinib treatment
Chronic obstructive pu
Viral respiratory disease
Cirrhosis, hepatic insuff
Other (diabetes, chroni
Fever refractory to > 3 c
Pleuritic chest pain
Dyspnea
Hemoptysis
Respiratory insufficienc
CT scan of the lung
Chest X-ray
Air-crescent sign
Cavity
Dense, well-circumscri
Diffuse reticular and al
Nonspecific infiltrates a
Pleural fluid
Wedge-shaped infiltrat
Tree-in-bud pattern
Positive direct examina
Positive *Aspergillus* cult
Positive *Aspergillus* cult
BALF galactomannan
BALF *Aspergillus* qPCR
Serum/plasma galacto
Serum/plasma *Aspergil*

* Two consecutive qPCR tests positive in blood, or one qPCR test positive in blood and one qPCR test positive in BALF

13.30-14.35	**Soru(n)larla İnvazif Aspergilloz** Oturum Başkanları: **İlkay KARAOĞLAN, Süda TEKİN**
13.30-13.55	İnvazif Aspergilloz Tanısına Yaklaşım **Yasemin TEZER-TEKÇE**
13.55-14.20	İnvazif Aspergillozun Güncel Tedavisi **Şafak KAYA**
14.20-14.35	Tartışma

Page 1

Probable/putative	Host fa factor+ al facto
Possible	Host fa factor
Colonisation	

Table S2: comparison of probable/putative, possible and colonisation diagnosis

Intensive Care Med (2024) 50:502–515
https://doi.org/10.1007/s00134-024-07341-7

CONFERENCE REPORTS AND EXPERT PANEL

Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM

Matteo Bassetti[1,2*], Daniele R. Giacobbe[1,2], Christina Agvald-Ohman[3], Murat Akova[4], Ana Alastruey-Izquierdo[5,6], Sevtap Arikan-Akdagli[7], Elie Azoulay[8,9], Stijn Blot[10,11], Oliver A. Cornely[12,13,14,15],

Yoğun bakım ünitesinde yatan, nötropenik olmayan yetişkin hastalarda **kanıtlanmış** invaziv aspergilloz için **araştırma tanımı**

Definition of proven invasive aspergillosis

Consensus reached after two rounds of remote voting and one round of live meeting voting (93% agreement)

Proven invasive aspergillosis is defined by at least one of the following

Tissue invasion shown by histological or cytopathological evidence on a specimen obtained from a normally sterile site or the lung with biopsy or needle aspiration, combined with detection of hyphae compatible with *Aspergillus* spp. (confirmed by culture or PCR)

Recovery of *Aspergillus* spp. by culture on a specimen obtained from a normally sterile site by means of biopsy or needle aspiration, from a lesion consistent with an infectious process

- Steril bölgelerden bx veya iğne aspirasyon gibi yöntemlerle alınan örneklerde histopatolojik incelemede Aspergillus hifleri ile uyumlu doku invazyonunun gösterilmesi + kültür ve PCR ile konfirme edilmesi
- Enfeksiyöz süreçte, steril bölgelerden alınan biyopsi materyal kültürlerinde *Aspergillus spp* üremesi

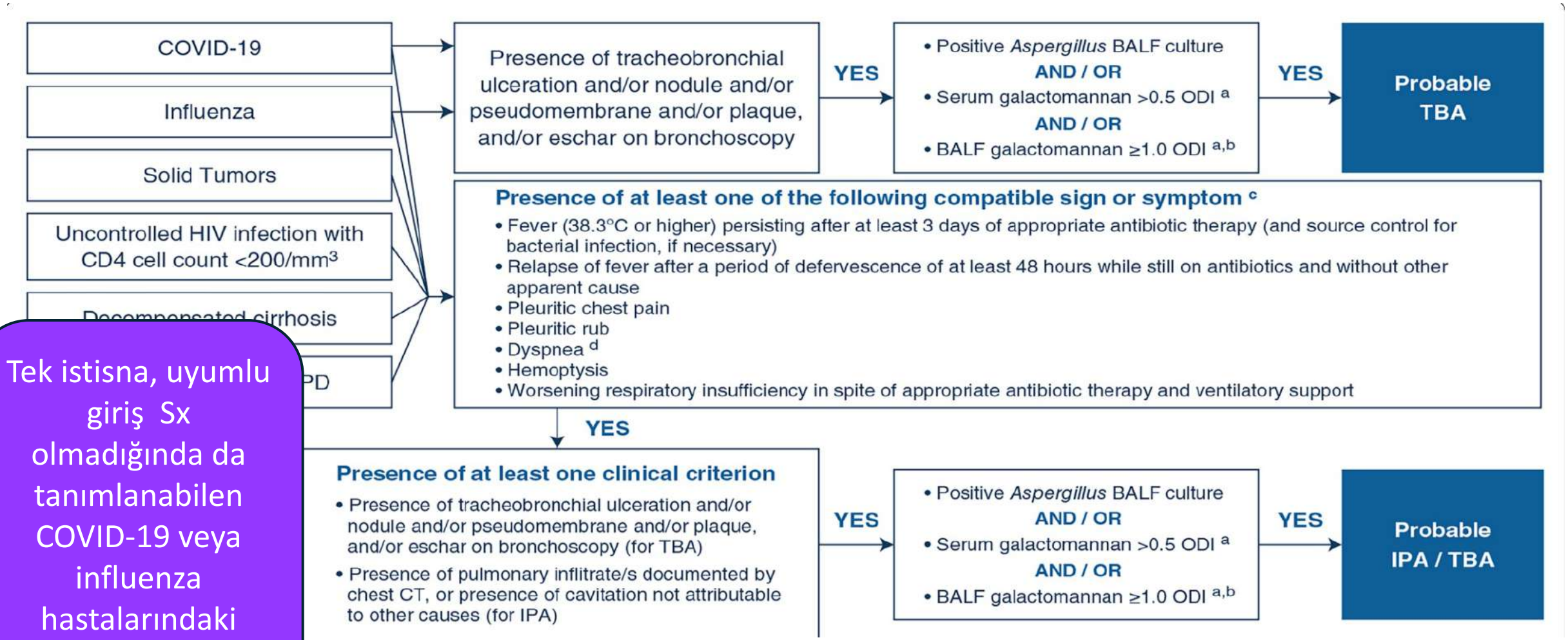
Yoğun bakım ünitesinde yatan, nötropenik olmayan, yetişkin hastalarda **muhtemel invaziv** pulmoner aspergilloz ve trakeobronşiyal aspergilloz için **araştırma tanımları**

Definitions of probable IPA and probable TBA
Consensus reached after three rounds of remote voting and three rounds of live meeting voting (84% agreement)
Evaluation for defining probable IPA and probable TBA in research studies should be performed only in patients with at least one of the following compatible signs and symptoms (precondition for evaluation)
Compatible signs and symptoms
Fever (38.3 °C or higher) persisting after at least 3 days of appropriate antibiotic therapy (and source control for bacterial infection, if necessary)
Relapse of fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
Pleuritic chest pain
Pleuritic rub
Dyspnea[a]
Hemoptysis
Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
Patients with at least one compatible sign or symptom should be evaluated for the presence of at least one of the following ICU host factors for probable IPA and probable TBA
ICU host factors
Influenza
COVID-19
Moderate/severe COPD
Decompensated cirrhosis
Uncontrolled HIV infection with CD4 cell count < 200/mm^3
Solid tumors
In patients with at least one compatible sign or symptom and at least one entry criterion, probable IPA or probable TBA are defined by the presence of at least one clinical criterion and at least one mycological criterion
Clinical criteria
Presence of tracheobronchial ulceration and/or nodule and/or pseudomembrane and/or plaque, and/or eschar on bronchoscopy (for defining probable TBA[b])
Presence of pulmonary infiltrate/s documented by chest CT, or presence of cavitation not attributable to other causes (for defining probable IPA)
Mycological criteria
Positive *Aspergillus* BALF culture
Serum galactomannan > 0.5 ODI[c]
BALF galactomannan ≥ 1.0 ODI[c,d]

Uygun klinik belirti ve bulgulardan(***giriş kriterleri***) en az biri olan, en az bir uygun YBÜ **konak faktörlerini** sağlayan hastada;
En az 1 klinik (***görüntüleme, bronkoskopi***) ve 1 mikolojik kriter (***BAL PCR,BAL/serum galaktomannan)*** varlığı olması

Olası İPA /TBA tanımını kar şeması

Olası IPA/TBA tanımları, EORTC/MSGERC konsensüsünde tanımlandığı şekilde konak faktörlerini karşılayan yoğun bakım hastaları için geçerli değildir!



Tek istisna, uyumlu giriş Sx olmadığında da tanımlanabilen COVID-19 veya influenza hastalarındaki muhtemel TBA'dır

FUNDICU; PCR ve LFA hakkında…

- **Aspergillus PCR** ile ilgili olarak; **BALF, serum, plazma ve/veya tam kanda** kullanımı,(ECMM **olası)** IPA/TBA'lı hastaları belirlemek ve erken tedaviyi teşvik etmek için önceki kılavuzları destekler nitelikte, klinik uygulamada yararlı olabileceği belirtilmiş.

- *Aspergillus* lateral flow device (AspLFD) ve GM lateral flow assay de yararlı olabileceği belirtilmekte.

İnvaziv Aspergillozda Tanı

Risk faktörlerine göre, **(şüphe eşiği düşük, araştırma eşiği yüksek)**

- Histopatolojik
- Mikrobiyolojik
- Seroloji
- Görüntüleme

Test	Microscopy Histology	Culture	Biomarkers	Molecular
Time	10 min-3-7 days	3-28 days	1-3 h	5-72 h
Pros	✓ Fast ✓ Invasion	✓ Specific ✓ Epidemiology ✓ AFST	✓ Fast ✓ Invasion ✓ POC available	✓ Fast ✓ Invasion
Cons	❖ Sensitivity ❖ Expertise	❖ Slow ❖ Sensitivity	❖ Specificity ❖ Availability	❖ Complex ❖ Non sterile samples?

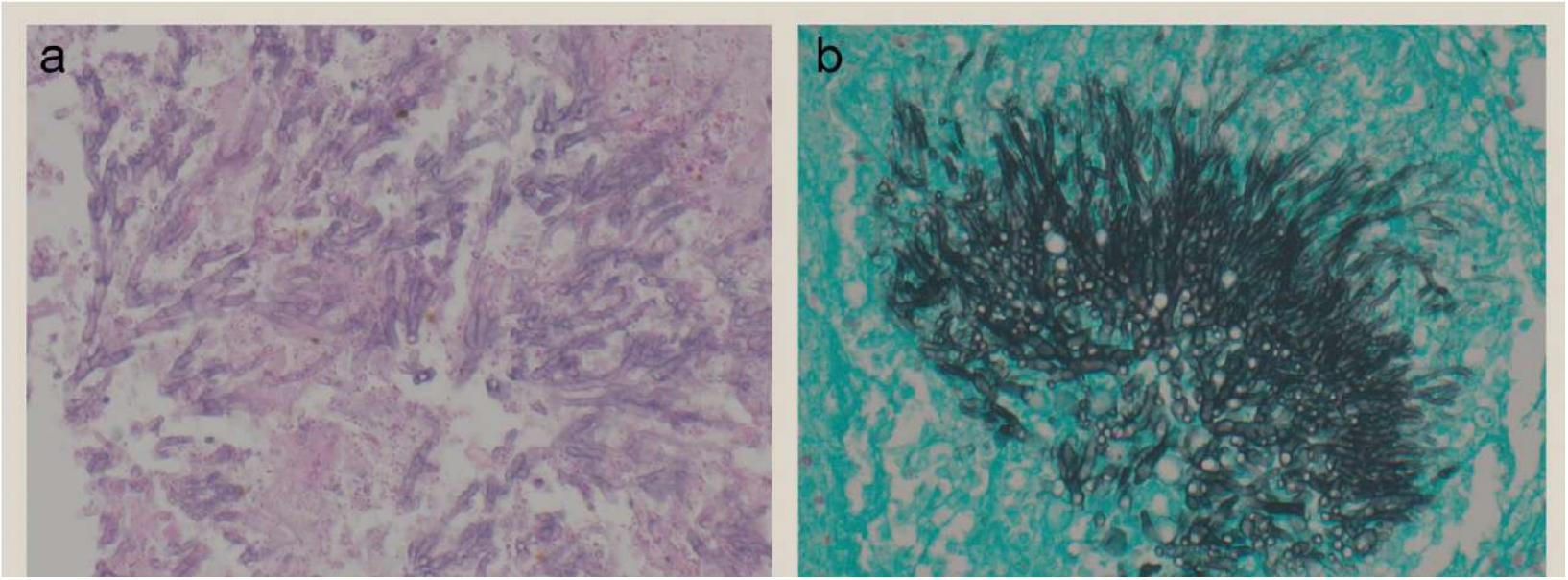
Tanı

- Bağışıklık sistemi baskılanmış hastalarda mantar enfeksiyonlarının **teşhisi zordur,** çünkü mevcut teşhis yöntemleri **duyarlılık ve özgüllükten yoksun olabilir** veya klinik olarak yararlı bir sonuç vermek **için çok uzun sürebilir**. Belirti ve **semptomlar spesifik değildir**, mantar **kolonizasyonunun invazif hastalıktan ayırt edilmesi zordur, kan kültürleri** sıklıkla **negatiftir** ve hastalar **invazif tanısal** girişimler **yapılamayabilir.**
- **Mikroskopi ve kültür referans** standart olmaya devam etmektedir ; tanı verimini artırmak için geleneksel yöntemlerle birlikte kültüre dayalı olmayan tekniklerin kullanılması önerilmektedir
- Fungal **patojenin bilinmesi** uygun **antifungal** tedaviye, dozuna ve tedavi süresine **rehberlik edecektir.**

PATOLOJİK TANI

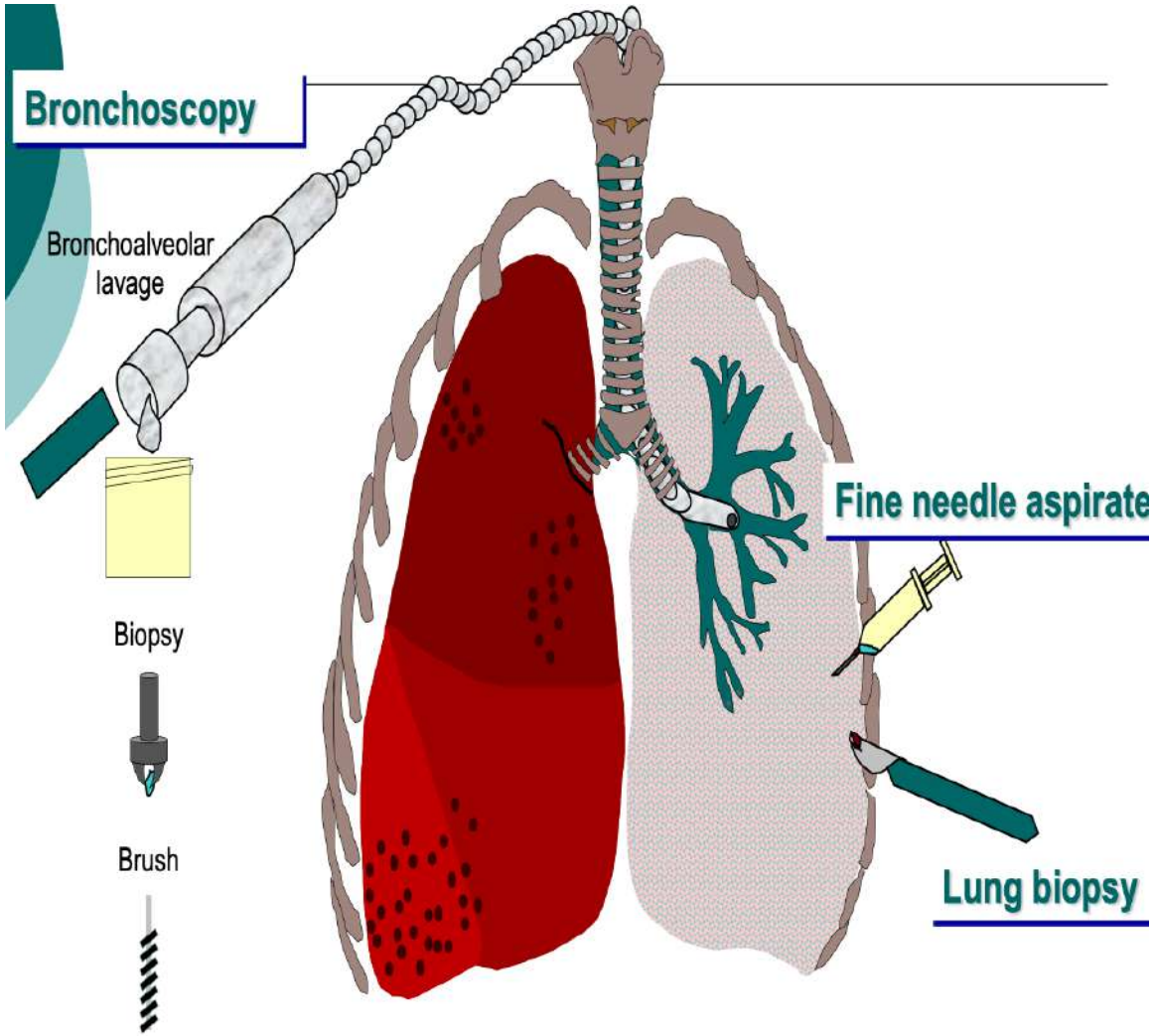
A histopathological approach to diagnosis and classification of invasive fungal infections

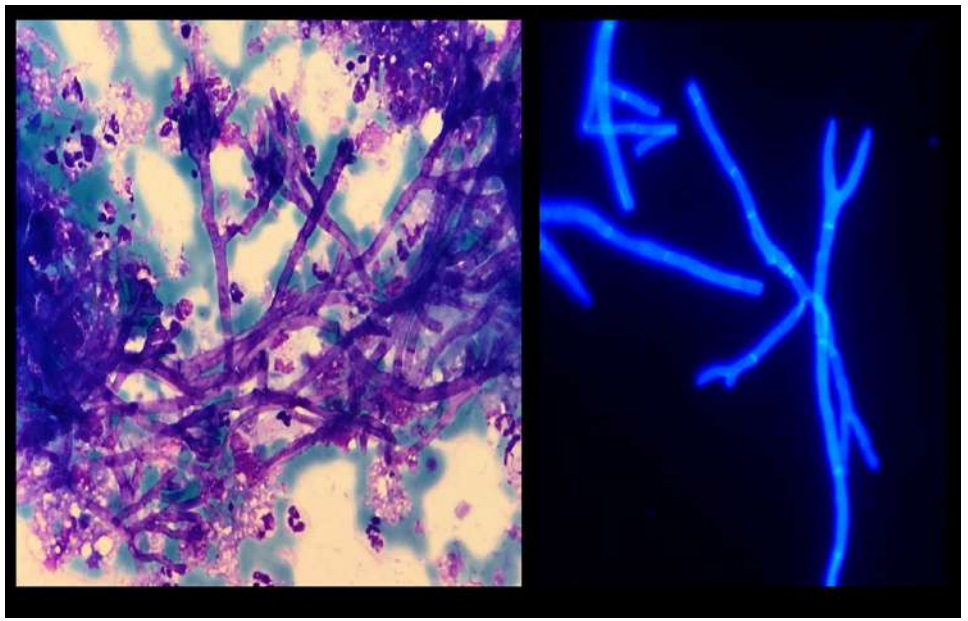
Vivek Sekhawat



Doku invazyonu , hemorajik nekroz angioinvazyon

PAS ve Grocott boyaX200 büyütmede,
45 derece açı ile dallanan düzenli septalı dikotom

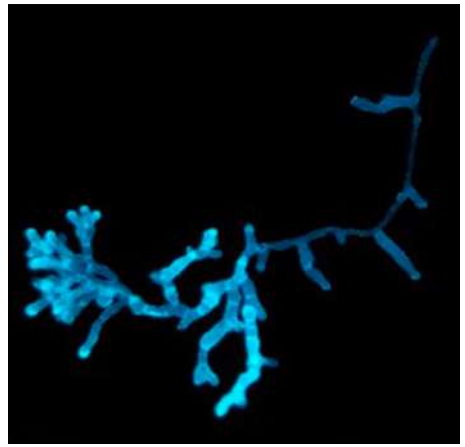




Dalak apsesiden alınan örnekte A. fumigatus

Medical Mycology, 2019, Vol. 57, No. S2

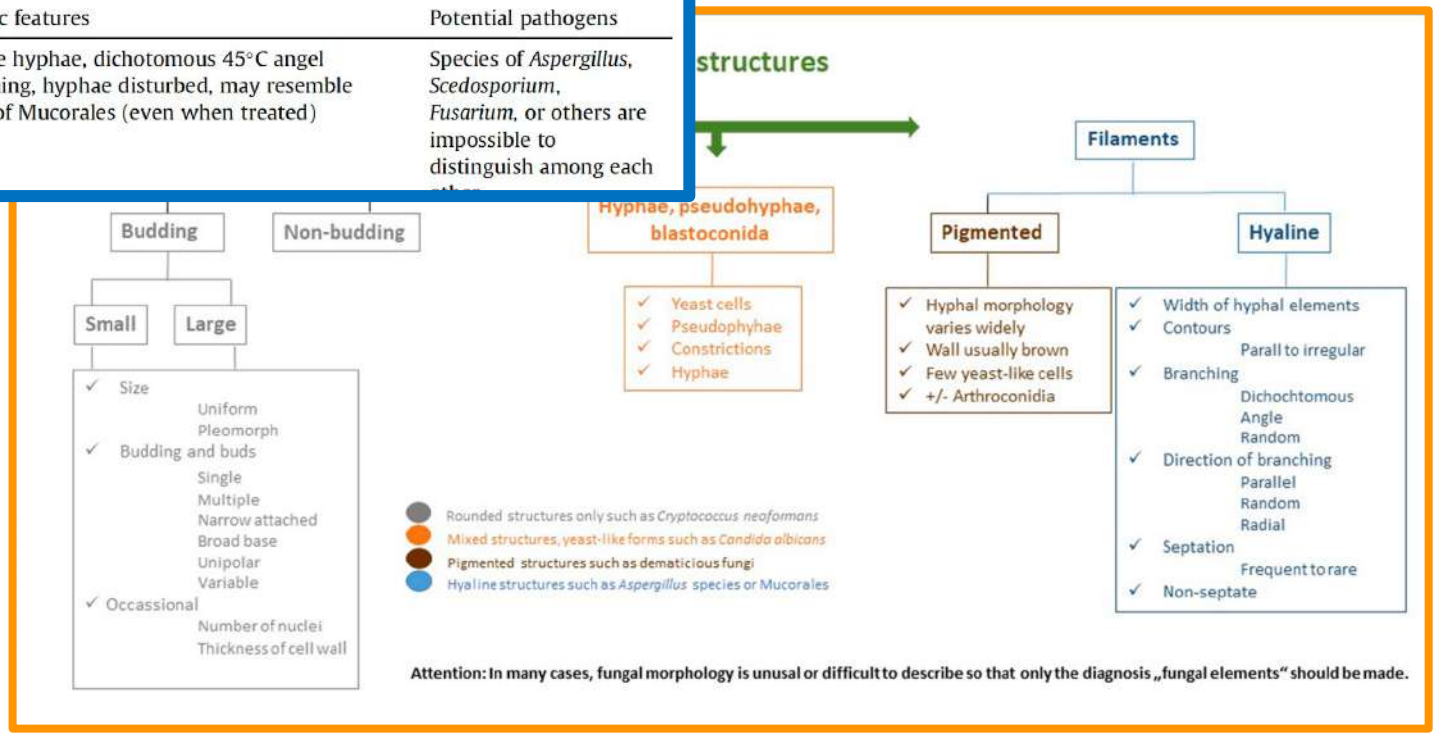
Mikrobiyolojik Tanı-Direk Mikroskobi ve Kültür



Potential fungal pathogens	Clinical specimens								
	Blood	Bone marrow	Cerebrospinal fluid	Synovial fluid	Eye	Urine	Respiratory tract	Skin and mucous	Systemic sites
Yeasts	++++	+	+(+)	+	+	+++	+	+++	+++
Candida spp.	+++	+	++++	-(+)	+	++	+++	+	++
Cryptococcus neoformans	++++	+	++++	—	+	++	+++	++	+++
Trichosporon sp.	++++	—	—	—	—	—	+	+++	+
Malassezia sp.									
Hyaline moulds	+[b]	—	+(+)	—	+	+	+++++	++	+++
Aspergillus sp.	—	—	(+)	—	+	—	++++	++	+++
Mucorales	+++	—	—	+	+(+)	—	++	+++(+)	++(+)
Fusarium sp.									

	Characteristic fungal elements	Sizes and diameter (μm)	Specific features	Potential pathogens
	Hyaline septate hyphae	3–12	Septate hyphae, dichotomous 45°C angel branching, hyphae disturbed, may resemble those of Mucorales (even when treated)	Species of *Aspergillus*, *Scedosporium*, *Fusarium*, or others are impossible to distinguish among each

KÜLTÜR; Steril doku örnekleri dışında kolonizasyon enfeksiyon ayırımı güç,
Derin doku örneği almak her zaman kolay değil
Küf enfeksiyonlarında duyarlılık düşük
Nispeten GEÇ SONUÇ
TÜR DÜZEYİNDE TANIMLAMA ve ANTİFUNGAL DUYARLILIK



M.A. Knoll et al. / Clinical Microbiology and Infection 29 (2023) 1031–1038

İPA Tanısında Kültür Dışı Ticari Testler ve Özellikleri

Target	Type of test (manufacturer)	Technique	Spectrum of detection	Type of sample	Cut-off
Galactomannan	Platelia™ *Aspergillus* EIA (Bio-Rad)	Immunoenzymatic sandwich assay	All *Aspergillus* species (specific)[#]	Serum, BAL	0.5–1.0 ODI[¶]
	Soña *Aspergillus* galactomannan LFA (IMMY)	Immunochromatographic assay (LFA)			Visual reading or cube reader: 0.5–1.0[¶] (index values)
	Aspergillus galactomannan VirClia™ (Vircell)	Chemoluminescent assay			1.0 (index value)
(1→3)-β-D-Glucan	Fungitell™ (Associates of Cape Cod)	Colorimetric assay (microplate)	All *Aspergillus* species (not specific)[+]	Serum	60–80 pg·mL^{-1}[§]
	Fungitell STAT™ (Associates of Cape Cod)	Colorimetric assay (single tube)			0.75–1.2 (index values)[§]
	Wako β-glucan test (Fujifilm Wako Chemicals)	Turbidimetric assay (single tube)			7.0 pg·mL^{-1}
	Dynamiker Fungus (1–3)-β-D-glucan (Dynamiker Biotechnology)	Colorimetric assay (microplate)			70–95 pg·mL^{-1}[§]
***Aspergillus* DNA**	MycAssay *Aspergillus*™ (Myconostica Ltd., now Microgen Bioproducts Ltd.)	Real-time PCR (18S rDNA)	Most relevant *Aspergillus* species	BAL, other respiratory samples, serum	NA
	AsperGenius™ (PathoNostics)	Multiplex real-time PCR (28S rDNA and *Cyp51A*)	Most relevant *Aspergillus* species, *Cyp51A* mutations (L98H, TR34, T289A, Y121F)		NA
	MycoGenie™ (AdemTech)	Real-time PCR (28S rDNA and *Cyp51A*)	*Aspergillus fumigatus*, *Cyp51A* mutations (L98H, TR34)		NA
	Fungiplex *Aspergillus* azole-R™ (Bruker Daltonics GmbH)	Multiplex real-time PCR	*Aspergillus* species, *Cyp51A* (TR34, TR46)		NA

Eur Respir Rev 2022; 31: 220114

KÜLTÜR DIŞI MİKROBİYOLOJİK TANI

- **Galaktomannan**, mantar büyümesi sırasında salınan ve daha sonra serum ve diğer vücut sıvılarında tespit edilebilen bir Aspergillus hücre duvarı polisakkaritidir

- GM tespiti, EIA gibi farklı tekniklerle veya lateral flow device (LFD) ve lateral flow assay (LFA) gibi yatak başı (POC) testleriyle mümkündür.

- Farklı ticari testler bulunmaktadır.

Galaktomannan

Method	Indication	Comments	
		Technical features	Limitations
Galactomannan (GM) and galactomannan protein (GP) testing via EIA Commercial assays - Bio-Rad GM-EIA™ - Immy GM-EIA™ - Euroimmun™GM-EIA	To detect GM antigen of serum and BAL To detect early IA in high-risk patients (screening test) who are not on active mould prophylaxis Part of EORTC/MSG criteria (positive GM in combination with host factor and clinical criteria), recommendations: 2 × serum samples/week with cut-off >0.5 1 single sample, positive cut-off >0.7 To detect GM in BAL samples (target diagnostic test): cut-off value ≥ 1 Prospective monitoring of GM levels 2 × weekly in high-risk paediatric population Few studies investigated urine GM/creatinine ratio EORTC/MSG criteria support similar GM thresholds for adults and children	Serum GM sensitivity (56%–89%) and specificity (67%–99%), cut-off >0.5 Ongoing serum cut-off value > 1.4: sign of therapeutic failure; mortality of 48% in haematological patients BAL GM sensitivity (88%) and specificity (81%) cut-off ≥1 A BAL urea-diluted and normalized cut-off of 2.94 resulted in a specificity of 86% and sensitivity of 94% BAL GM better diagnostic performance on mould-active prophylaxis Quantification in CSF* (>0.5) is useful, but not standardized and validated Immy GM-EIA and Bio-Rad GM-EIA provided comparable data when testing serum Immy GM-EIA: reducing the threshold to ≥0.27 generated sensitivity and specificity of 90% and 92% Euroimmun GM-EIA and Bio-Rad GM EIA provided similar results when testing serum	Some *Aspergillus* are poor GM producer, cross reactivity with other fungal pathogens (*Fusarium*, *Paecilomyces*, *Trichoderma*, *Histoplasma* and *Penicillium* species), serum GM EIA was positive in 73% in patients with invasive fusariosis Decreased prognostic value in non-neutropenic patients Mould-active antifungal therapy does impact sensitivity, specifically when testing serum Suggestion: cut-off value > 0.3 increased sensitivity to 90% (Bio-Rad GM-EIA) False-positive results reported due to ingestion of ice-pops, transfusion, plasma lyte infusion Piperacillin/tazobactam may no longer cause false-positive results High prevalence of peribronchial focal lesions of airway IA in neutropenic patients and serum GM levels: 17 proven cases showed negative serum GM, but 14 CT findings Low diagnostic yield of serum testing in influenza-associated IA The values of urine GM-to-creatinine ratio needs further evaluation

- Aspergillus dışı nedenlerle de pozitif (cross rxn, false + antijenemi ve ilacalar…)
- Cut-off serum>0.5
  BAL>1
  CSF>0.5

Clinical Microbiology and Infection 27 (2021) 1230–1241

Journal Pre-proof

Cerebrospinal fluid galactomannan detection for the diagnosis of central nervous system aspergillosis: a diagnostic test accuracy systematic review and meta-analysis

Adam S. Komorowski, MD, Clayton W. Hall, MD PhD, Sukhreet Atwal, BSc, Rochelle Johnstone, MD MA FRCPC, Robert Walker, III, MD MS, Dominik Mertz, MD MSc, Eva A. Piessens, MD MPH, Deborah Yamamura, MD FRCPC, Ekkehard M. Kasper, MD DPhil FACS FAANS FRCSC

SSS Aspergillozunda BOS Galaktomannan

CSF galaktomannan CNS aspergillozunda tanısal değerini belirlemek için,
Toplam 342 hasta ve bunların 91'i EORTC/MSGERC kriterlerine göre kanıtlanmış veya muhtemel CNS aspergillozu.

CSF galaktomannanın testi özgüllük iyi ancak düşük duyarlılık sağladığı için
bunun bir **dışlama testi olarak kullanımını sınırlı.**

İmmunkompetan hastalarda iyi NPV, immünkompromize hastalar için yüksek PPV yüksek

Bu sonuçlar CSF galaktomannanın **tanısal bir bileşen olarak kullanılmaya devam edilmesini desteklemektedir.**

Lateral flow *(Endikasyon, Teknik özellik ve Kısıtlılıkları)*

Lateral flow device (LFD, Ohm™) (detects an extracellular mannoprotein)	To diagnose IA in serum, BAL Qualitative and quantitative (reader) detection Evaluated in mixed immunocompromised populations and non-neutropenic patients	Simple, rapid (15 min), digital read-out may slightly improve data Serum LFD sensitivity (62%) and specificity (68%) in chronic aspergillosis BAL LFD sensitivity (89%–100%) and specificity (81%–88%) in probable and proven IA cases Mixed population: BAL sensitivity (64%) and specificity (87%), blood sensitivity (20%) and specificity (91%) Head-to-head comparison of LFD and LFA from BAL samples of haematological patients showed identical specificity for both assays, sensitivity (83% versus 69%) and negative predictive value (89 versus 82%) was better for LFA	Time of reading (15 min) seems to be crucial, no pretreatment necessary Cross reaction with *Penicillium* sp BAL LFD under mould-active prophylaxis was 56%, without was 86% in hematological patients LFD and LFA form BALs had comparable results: sensitivity (58%–69%) and specificity (68%–75%) Mannoprotein detection in BALs from organ transplantation patients shows a poor performance Two small studies (8 proven cases) showed LFD resulting with sensitivity of 25%–38% in BALs; since then the LFD assay was improved
Lateral flow assay (LFA, Immy™) (detects GM)	To diagnose of IA in serum and BAL Qualitative and quantitative (reader) detection Evaluated in mixed immunocompromised populations and non-neutropenic patients	Simple, rapid (30 min), digital read-out may slightly improve data Mixed population: BAL sensitivity (77%) and specificity (81%), blood sensitivity (70%) and specificity (96%) BAL LFA sensitivity (92%) and specificity (91%) in culture positive samples BAL LFA using a cut-off of 1.5 resulted in a sensitivity of 74% and specificity of 83% LFA and Bio-Rad GM-EIA show similar results, total agreement with LFA cube reader (cut-off 1) was 84% LFA performance was consistent across different patient	Sample pretreatment is necessary Cross reaction with BALs and positive culture with *Scedosporium* sp., *Fusarium* sp., *Saccharomyces cerevisiae*, *Candida parapsilosis*, *Geotrichum* sp.
Lateral flow urine assay (using the galactofuranose-specific monoclonal antibody mAb476)	To detect urine antigens from *A. fumigatus*	Urine detection: sensitivity (80%) and specificity (92%)	Limited data are available, further validation is needed
Exhaled breath condensate (EBC)	To detect GM, to diagnose IA	GM is detectable in EBC EBC optical density values were significantly higher than in healthy volunteers	No correlation of EBC values with diagnosis of IA No correlation of EBC GM-EIA and BAL GM-EIA

LFA (Galaktomanan)
LFD (JF5 mannoprotein)
Her ikisi de serum ve BAL'da
LF urine: idrarda monoklonal antikor (valide değil)
Nefes testi? (GM)

Clinical Microbiology and Infection 27 (2021) 1230–1241

Beta-D-Glukan testi

Method	Indication	Comments	
		Technical features	Limitations
β-D-glucan test (BDG) Commercial assays (all have different cut-offs)*: - Fungitell™ (colorimetric) - Glucatell Test™ (colorimetric) - Wako-BDG™ (turbidimetric) - Dynamiker Fungus™ (turbidimetric) - Fungitec-G™ (colorimetric) - B-G Star (colorimetric) - Fungitell STAT™ (colorimetric)	To diagnose IFD from serum To screen for IFD from serum *Fungitell assay: FDA approved, cut-off 80 pg/mL for a positive test and <60 pg/mL for a negative test, designed for batch testing of up to 21 patients: not suitable for small institutions with low sample numbers Wako BDG: 11 pg/mL; Dynamiker: 70–100 pg/mL Fungitell: 60–80 pg/mL, Fungitec G-Test 20 pg/mL, B-G Star: 11 pg/mL Fungitell STAT new rapid test that can be run on one or more patient specimens (single sample testing) Monitoring of BDG in high-risk patients: 2–3 × per week among onco-haematological patients or or in patients during the neutropenic phase Should be used as part of a multi-diagnostic approach, targeted testing in combination with PCR and GM BDG detection via Fungitell is part of EORTC/MSG criteria (positive serum BDG in combination with host factor and clinical criterion) in certain patients	Panfungal marker: detects many relevant fungal genera including *Aspergillus*, *Candida*, *Pneumocystis*, *Trichosporon*, *Fusarium* and *Exserohilum* Repetition of serum samples testing increase specificity (from 80–97%) Immunocompromised or at-risk patients: Fungitell ™assay: 78-80% sensitivity, 63 - 81% specificity Mixed population: Dynamiker™ assays: 64-81% sensitivity, 78- 80% specificity; Glucatell ™assay: 50 -92% sensitivity, 41-94% specificity; Wako-BDG ™assay: 50 - 86% sensitivity, 89-100% specificity; Fungitec-G ™assay: 67-88% sensitivity, 60-85% specificity More sensitive than blood cultures for deep-seated candidiasis (62% vs. 17%), anticipates diagnosis of intra-abdominal candidiasis High negative predictive value for invasive candidiasis (IC) in low prevalence settings Better diagnostic value for high-risk patients with hematological malignancies and chemotherapy-induced neutropenia or allogeneic HSCT, sensitivity (60–80%) and specificity around 90% High sensitivity of 89% for BDG in neonatal IC, 60% specificity High sensitivity (91%) of serum BDG testing for *Pneumocystis jirovecii* pneumonia (specificity 79%) Off-label use for cerebrospinal fluid in fungal meningitis: 53%–100% sensitivity and 82%–98% specificity for different species	Does not detect Mucorales, *Blastomyces dermatitidis* (yeast) or *Cryptococcus*, not specific for any fungal genus: additional identification necessary False negative: lipaemic and haemolysed blood samples (not valid for turbidimetric) Not suitable for the application on BAL to diagnose pulmonary IA Sensitivity for *Candida* is species dependent (72%–100%), reduced sensitivity for *Candida parapsilosis* infections (less fungal BDG) Heterogeneous results: depend on the type of populations, the method of testing (monitoring or punctual), cut-off and definition of positivity, and the inclusion or not of possible IA cases Patients at low or moderate risk of IA: sensitivity of 40% or less, low diagnostic accuracy Declines slowly in many cases of IA, IC and *Pneumocystis jirovecii* pneumonia with appropriate therapy (no monitoring of treatment response), persistence above the threshold for positivity after clinical clearance of the original infection Limited data in paediatric population, optimal cut-off in neonates and children is unknown, as mean BDG levels are higher in immunocompetent children than in adults Klicken oder tippen Sie hier, um Text einzugeben. False positivity in haemodialysis, surgical gauze products, bacteraemia, antifungals, intravenous antibiotic therapy (e.g. amoxicillin-clavulanic acid) or blood products, high risk of external contamination Fungitell STAT: clinical validation still needed

Mercier *et al. Crit Care* (2020) 24:642
https://doi.org/10.1186/s13054-020-03367-7

Critical Care

RESEARCH Open Access

Point of care aspergillus testing in intensive care patients

Erişkin YBÜ'de BAL Aspergillus Lateral flow assay sonrası; tanımlamalara bağlı olarak **duyarlılık** 0.88-0.94 iken **özgüllük** 081, ROC eğrisi 0.90-0.94 (iyi performans)

Abstract

Background: Invasive pulmonary aspergillosis (IPA) is an increasingly recognized complication in intensive care unit (ICU) patients, especially those with influenza, cirrhosis, chronic obstructive pulmonary disease, and other diseases. The diagnosis can be challenging, especially in the ICU, where clinical symptoms as well as imaging are mostly non-specific. Recently, *Aspergillus* lateral flow tests were developed to decrease the time to diagnosis of IPA. Several studies have shown promising results in bronchoalveolar lavage fluid (BALf) from hematology patients. We therefore evaluated a new lateral flow test for IPA in ICU patients.

Methods: Using left-over BALf from adult ICU patients in two university hospitals, we studied the performance of the *Aspergillus* galactomannan lateral flow assay (LFA) by IMMY (Norman, OK, USA). Patients were classified according to the 2008 EORTC-MSG definitions, the AspICU criteria, and the modified AspICU criteria, which incorporate galactomannan results. These internationally recognized consensus definitions for the diagnosis of IPA incorporate patient characteristics, microbiology and radiology. The LFA was read out visually and with a digital reader by researchers blinded to the final clinical diagnosis and IPA classification.

Results: We included 178 patients, of which 55 were classified as cases (6 cases of proven and 26 cases of probable IPA according to the EORTC-MSG definitions, and an additional 23 cases according to the modified AspICU criteria). Depending on the definitions used, the sensitivity of the LFA was 0.88–0.94, the specificity was 0.81, and the area under the ROC curve 0.90–0.94, indicating good overall test performance.

Conclusions: In ICU patients, the LFA performed well on BALf and can be used as a rapid screening test while waiting for other microbiological results.

Keywords: Invasive aspergillosis, Diagnosis, Lateral flow assay, Galactomannan

Moleküler Testler

Molecular diagnostics for invasive fungal infections

Test	Pathogens	Sample Type	Advantages	Disadvantages	Comments
PCR					
Broad-range PCR	Wide range of fungal pathogens	Usually tissue	Can detect most pathogens	Less helpful in samples from non-sterile sites Poor performance in mixed infections Typically send-out	Sensitivity is best when fungi are visible on histopathology Fresh tissue samples have the highest sensitivity
Pathogen-directed PCR assays			Generally more sensitive than culture-based methods May permit an earlier diagnosis	Cost (variable) Difficult to reliably distinguish colonization from infection in airway samples	
	Aspergillus	BAL, serum	More sensitive than culture in BAL Some assays allow the detection of major azole resistance-associated mutations	Unable to distinguish colonization from infection from airway samples	
	Aspergillus, Mucorales (and *Nocardia*) +/– *Pneumocystis*	BAL	Syndromic testing allows testing of multiple pathogens with clinical overlap	Few published data Appears to have limited sensitivity Unable to distinguish colonization from infection	
Metagenomic Next-Generation Sequencing (eg, Karius)	Fungi (and bacteria, protozoa, algae, and DNA viruses)	Serum	Unbiased (agnostic) testing (can detect a pathogen even without a priori suspicion)	Cost (~$2000/test) Turn-around time (several days) Poor specificity (can detect small fragments of organisms, often with unclear significance)	

PCR:

- Hızlı sonuç
- Pahalı,
- Kolonizasyon /infeksiyon ayırımı??

Yeni Nesil Dizileme

Serum

Uzun süre

Pahalı

Hematolojik Maligniteli hastalarda Galaktomannan ve Aspergillus PCR Metaanaliz

Fungal biomarker	Study	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Serum			
GM	Pfeiffer *et al.* [38]	58 (52–64)	95 (94–96)
	Leeflang *et al.* [98]¶	78 (70–85)	85 (78–91)
	Arvanitis *et al.* [28]	92 (83–96)	90 (81–95)
PCR	Mengoli *et al.* [99]	88 (75–94)	75 (63–84)
	Arvanitis *et al.* [28]	84 (71–92)	76 (64–85)
GM and PCR#	Arvanitis *et al.* [28]	99 (96–100)	98 (94–100)
BAL			
GM	Guo *et al.* [100]¶	85 (72–93)	94 (89–97)
PCR			
	Avni *et al.* [29]¶	93 (70–98)	98 (93–99)
	Zou *et al.* [101]¶	82 (61–93)	98 (85–100)
	Heng *et al.* [30]	57 (31–80)	99 (60–100)
GM and PCR#	Avni *et al.* [29]¶	97 (83–99)	97 (93–99)
	Heng *et al.* [30]	84 (79–88)	94 (91–97)

Periyodik tarama ve tanı testlerinin çeşitliliğinin artırılması **tanı olasılığını artırıyor!**

Eur Respir Rev 2022; 31: 220114

Peki ne kadarını yapabiliyoruz?

The current state of laboratory mycology and access to antifungal treatment in Europe: a European Confederation of Medical Mycology survey

Jon Salmanton-García, Martin Hoenigl, Jean-Pierre Gangneux, Esther Segal, Ana Alastruey-Izquierdo, Sevtap Arikan Akdagli, Katrien Lagrou, Volkan Özenci, Antonio Vena, Oliver A Cornely

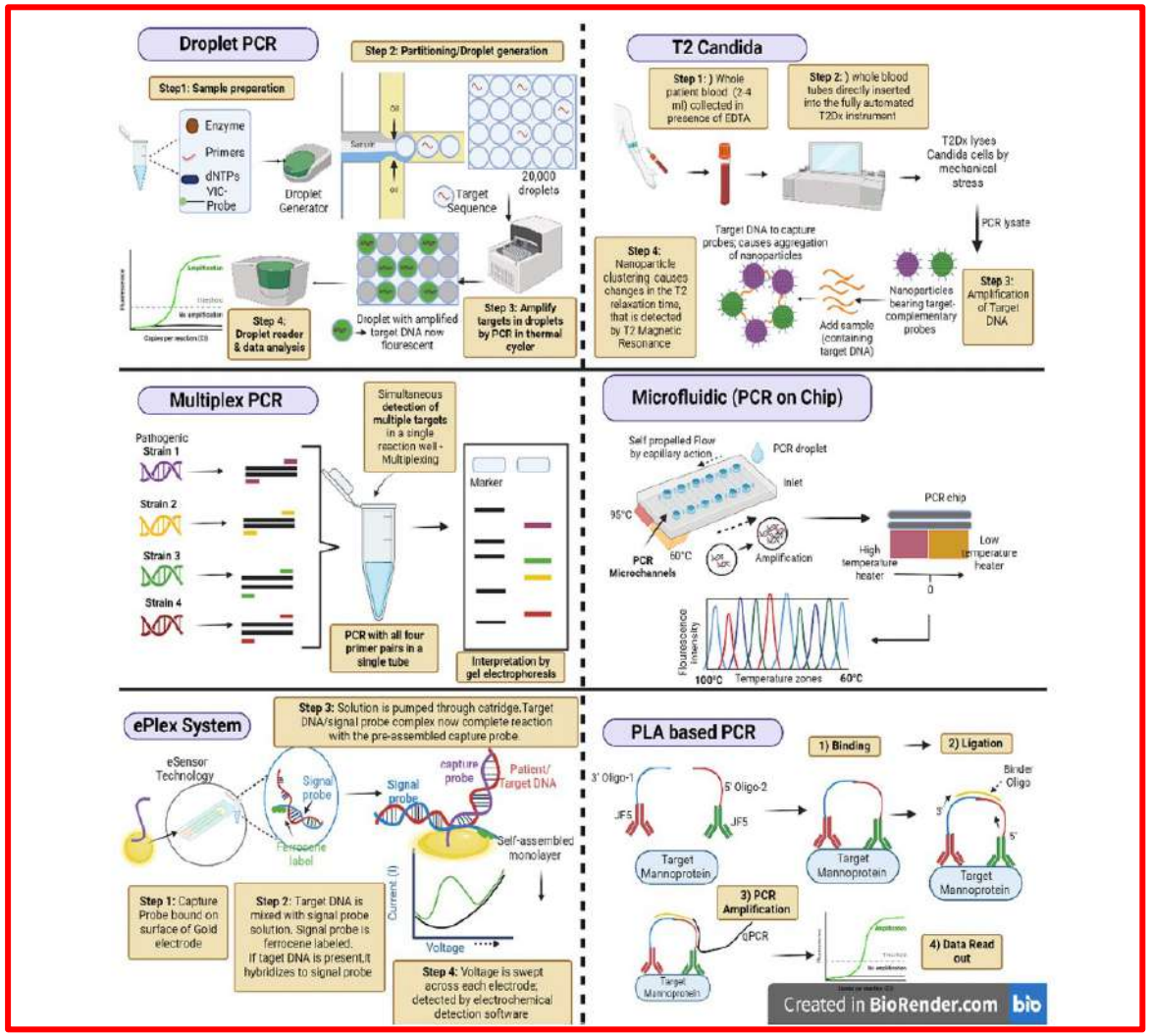
agement of invasive fungal infections. Lancet Microbe 2023; 4: e47–56

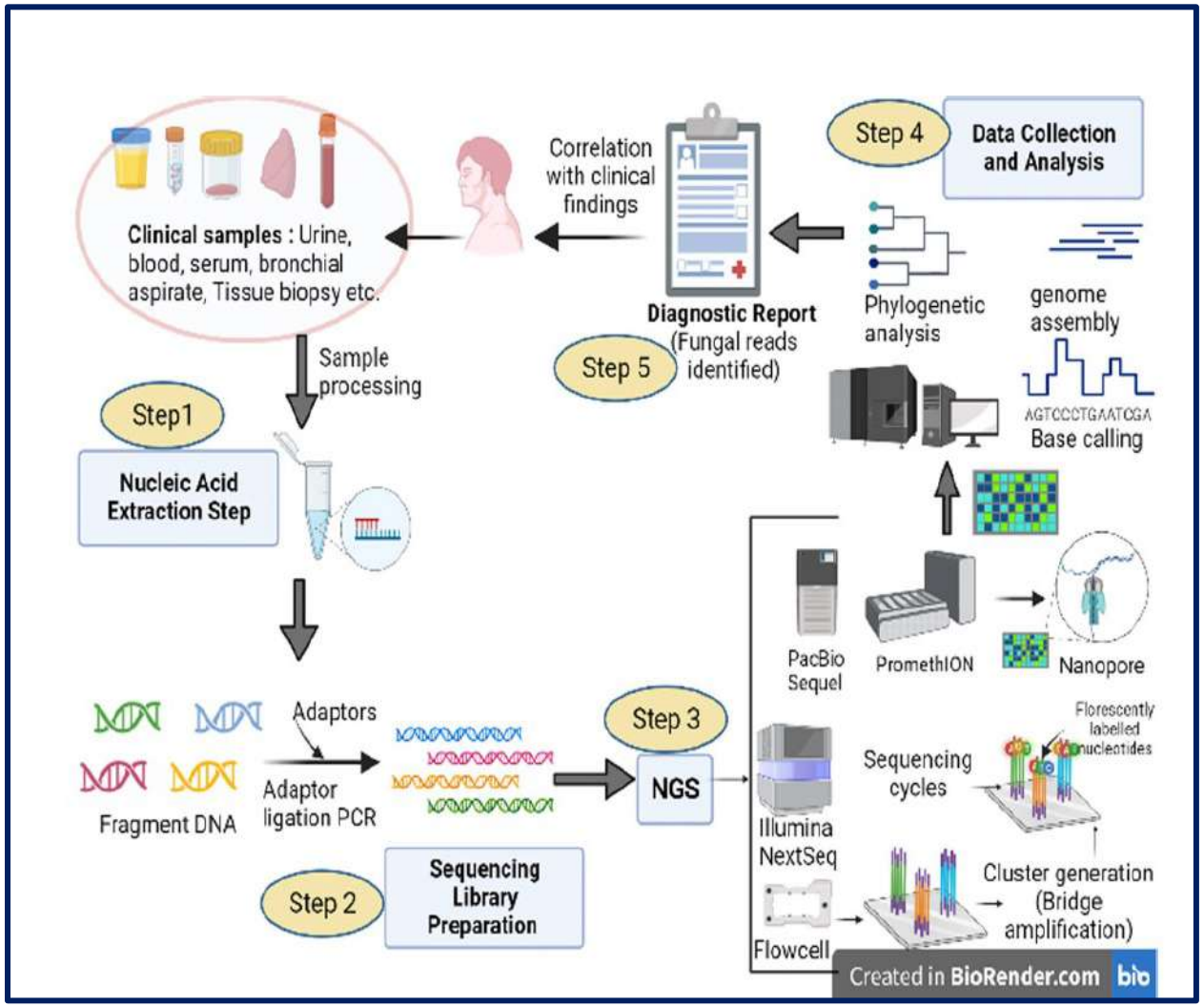
	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
Microscopy	375 (97%)	52 (96%)	162 (97%)	161 (96%)	0·93*
Staining dye					
Calcofluor white	180 (46%)	17 (31%)	64 (38%)	99 (59%)	<0·0001†
Giemsa stain	210 (54%)	30 (56%)	95 (57%)	85 (51%)	0·54†
China or India ink	303 (78%)	39 (72%)	137 (82%)	127 (76%)	0·22†
Potassium hydroxide	223 (57%)	25 (46%)	106 (63%)	92 (55%)	0·062†
Silver stain	147 (38%)	26 (48%)			
Others	191 (49%)	30 (56%)			
Direct microscopy frequency when invasive fungal infection is suspected					
Never	17 (4%)	4 (7%)			
Rarely	40 (10%)	7 (13%)			
Sometimes	40 (10%)	3 (6%)			
Often	70 (18%)	6 (11%)			
Always	220 (57%)	34 (63%)			
Direct examination in body fluids for suspected cryptococcosis	319 (82%)	38 (70%)			
Yes, India ink	259 (67%)	26 (48%)			
Yes, other stains	60 (15%)	12 (22%)			
Silver stain for suspected pneumocystosis	120 (31%)	22 (41%)			
Direct microscopy for suspected mucormycosis	211 (54%)	25 (46%)			
Culture and fungal identification	383 (99%)	51 (94%)			
Blood cultures for suspected fungemia	343 (88%)	36 (67%)			
Fungal culture media					
Niger seed agar (Bridseed agar)	46 (12%)	10 (19%)			
Candida chromogenic media	187 (48%)	20 (37%)			
Lactrimel agar	31 (8%)	3 (6%)			
Potato dextrose agar	148 (38%)	20 (37%)			
Sabouraud dextrose agar	293 (76%)	39 (72%)			
Sabouraud dextrose agar with chloramphenicol	245 (63%)	29 (54%)			
Sabouraud dextrose agar with gentamicin	175 (45%)	24 (44%)			
Selective agar (chloramphenicol with cycloheximide)	207 (53%)	21 (39%)			
Others	141 (36%)	13 (24%)			
Available tests for species identification	372 (96%)	47 (87%)			
Automated identification (ie, VITEK)	230 (59%)	39 (72%)			
Biochemical tests (conventional mycology)	208 (54%)	34 (63%)			
DNA sequencing	187 (48%)	13 (24%)			
MALDI-TOF MS	287 (74%)	17 (31%)	122 (73%)	148 (89%)	<0·0001†
Mounting medium	113 (29%)	12 (22%)	46 (28%)	55 (33%)	0·27†
Antifungal susceptibility tests	363 (94%)	50 (93%)	162 (97%)	154 (92%)	0·13*
Yeasts	113 (29%)	20 (37%)	53 (32%)	40 (24%)	..
Moulds	3 (1%)	2 (4%)	0	1 (1%)	..
Yeasts and moulds	247 (64%)	27 (50%)	109 (65%)	111 (66%)	..
Available antifungal susceptibility test technologies	363 (94%)	50 (93%)	162 (97%)	154 (92%)	0·13*
Broth microdilution, using CLSI standards	106 (27%)	15 (28%)	54 (32%)	37 (22%)	0·12†
Broth microdilution, using EUCAST standards	165 (43%)	22 (41%)	79 (47%)	64 (38%)	0·25†
Gradient strip tests	231 (60%)	23 (43%)	102 (61%)	106 (63%)	0·022†
VITEK	143 (37%)	23 (43%)	80 (48%)	40 (24%)	<0·0001†

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
(Continued from previous page)					
Molecular tests	329 (85%)	33 (61%)	138 (83%)	158 (95%)	<0·0001†
Aspergillus PCR	256 (66%)	25 (46%)	99 (59%)	132 (79%)	<0·0001†
Onsite	150 (39%)	14 (26%)	62 (37%)	74 (44%)	..
Outsourced	106 (27%)	11 (20%)	37 (22%)	58 (35%)	..
Candida PCR	210 (54%)	24 (44%)	83 (50%)	103 (62%)	0·027†
Onsite	100 (26%)	14 (26%)	51 (31%)	35 (21%)	..
Outsourced	110 (28%)	10 (19%)	32 (19%)	68 (41%)	..
Pneumocystis PCR	288 (74%)	24 (44%)	113 (68%)	151 (90%)	<0·0001†
Onsite	217 (56%)	16 (30%)	86 (51%)	115 (69%)	..
Outsourced	71 (18%)	8 (15%)	27 (16%)	36 (22%)	..
Mucorales PCR	182 (47%)	13 (24%)	59 (35%)	110 (66%)	<0·0001†
Onsite	76 (20%)	4 (7%)	24 (14%)	48 (29%)	..
Outsourced	106 (27%)	9 (17%)	35 (21%)	62 (37%)	..
Other molecular tests	185 (48%)	15 (28%)	64 (38%)	106 (63%)	..
Onsite	101 (26%)	8 (15%)	36 (22%)	57 (34%)	..
Outsourced	84 (22%)	7 (13%)	28 (17%)	49 (29%)	..

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
(Continued from previous page)					
Maximum identification capability					
Yeasts	388 (100%)	54 (100%)	167 (100%)	167 (100%)	..
Genus	17 (4%)	8 (15%)	4 (2%)	5 (3%)	..
Genus and species	177 (46%)	31 (57%)	84 (50%)	62 (37%)	..
Moulds	388 (100%)	54 (100%)	167 (100%)	167 (100%)	..
				(13%)	..
				(87%)	..
				(89%)	0·030†
				(84%)	0·037†
				(57%)	..
				(28%)	
				(69%)	0·0018†
				(36%)	..
				(34%)	..
				(65%)	<0·0001†
				(11%)	..
				(53%)	..
				(48%)	<0·0001†
				(2%)	..
				(46%)	..
				(95%)	0·010*
				(93%)	0·0035†
				(23%)	0·92†
				(13%)	..
				(10%)	..
				(90%)	0·061†
				(68%)	..
				(22%)	..
				(34%)	0·87†
				(23%)	..
				(11%)	..
				(56%)	0·047†
				(28%)	..
				(29%)	..
				(86%)	0·0001†
Cryptococcus LFA	188 (48%)	13 (24%)	71 (43%)	104 (62%)	<0·0001†
Onsite	138 (36%)	4 (7%)	53 (32%)	81 (49%)	..
Outsourced	50 (13%)	9 (17%)	18 (11%)	23 (14%)	..
Cryptococcus LAT	217 (56%)	29 (54%)	101 (60%)	87 (52%)	0·28†
Onsite	158 (41%)	16 (30%)	82 (49%)	60 (36%)	..
Outsourced	59 (15%)	13 (24%)	19 (11%)	27 (16%)	..
Histoplasma	133 (34%)	14 (26%)	41 (25%)	78 (47%)	<0·0001†
Onsite	28 (7%)	5 (9%)	10 (6%)	13 (8%)	..
Outsourced	105 (27%)	9 (17%)	31 (19%)	65 (39%)	..
β-glucan	236 (61%)	20 (37%)	91 (54%)	125 (75%)	<0·0001†
Onsite	123 (32%)	7 (13%)	53 (32%)	63 (38%)	..
Outsourced	113 (29%)	13 (24%)	38 (23%)	62 (37%)	..

Yakın gelecekte…





Journal of Biomedical Science (2023) 30:42

Current Clinical Microbiology Reports (2024) 11:51–61
https://doi.org/10.1007/s40588-024-00216-x

REVIEW

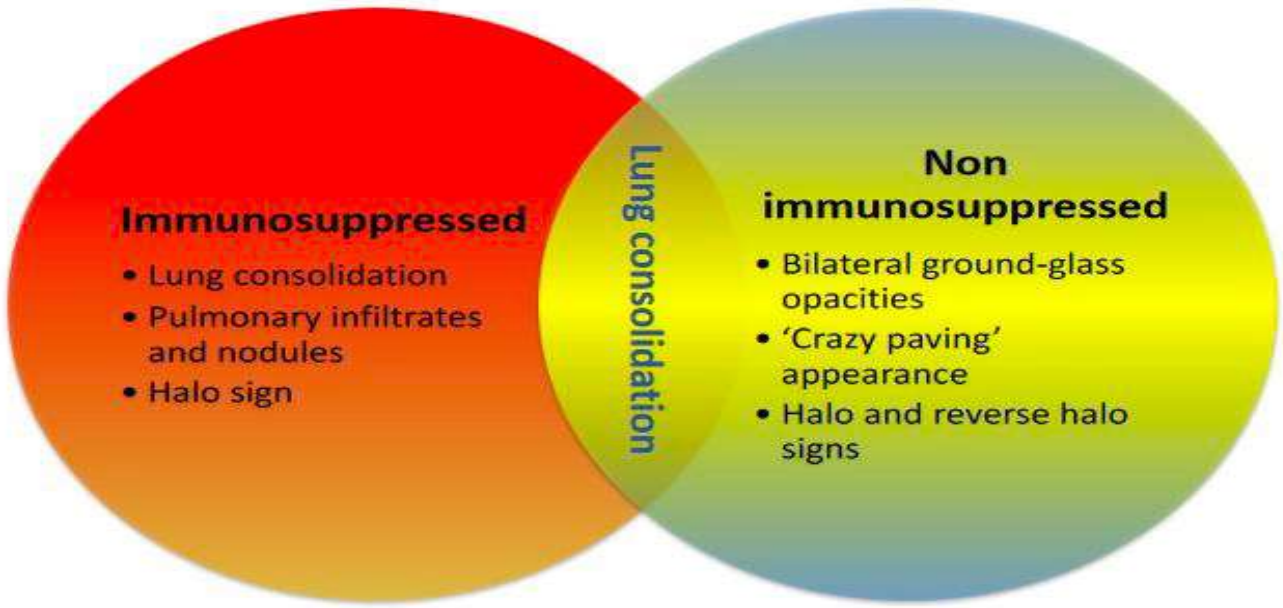
New Breath Diagnostics for Fungal Disease

Jenna Diefenderfer[1,2] · Heather D. Bean[1,2] · Emily A. Higgins Keppler[1,2]

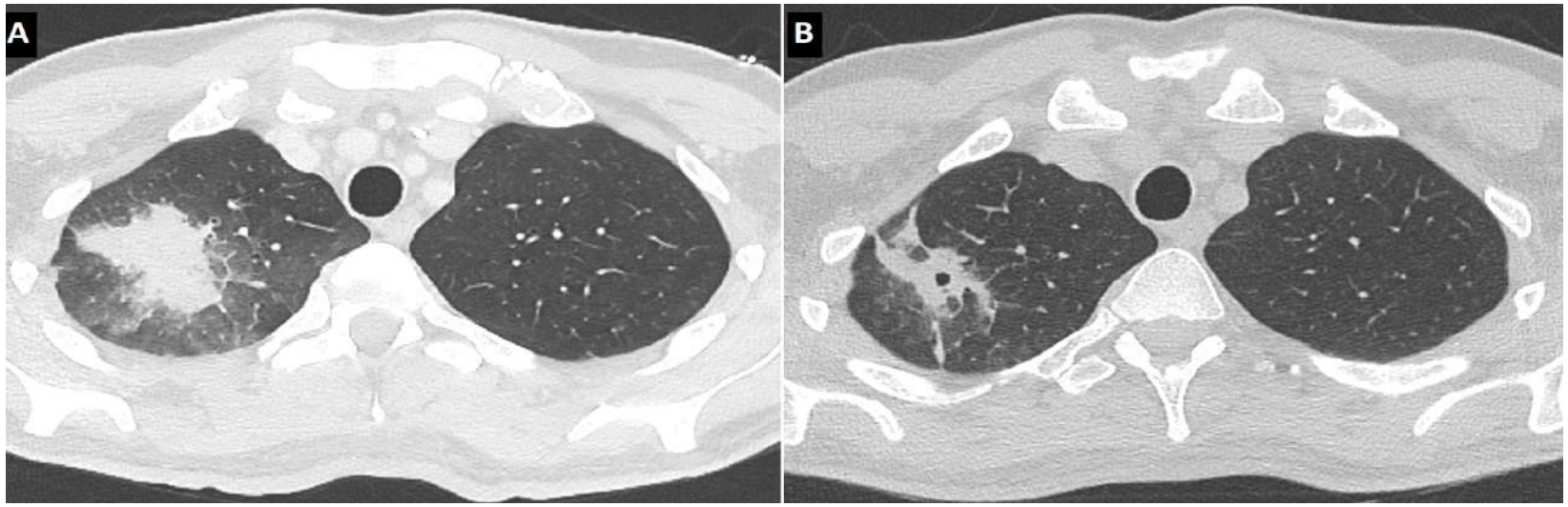
Genus	Species	Disease	Sample type			
			In vitro	Murine BALF	Murine breath	Human breath
Alternaria	*A. alternata*		[33]			
Aspergillus	*A. calidoustus*		[34]			
	A. flavus		[34]			
	A. fumigatus	Invasive aspergillosis	[34–41]		[42]	[34, 37, 43]
	A. niger	Invasive aspergillosis	[34, 37]			[34, 37]
	A. terreus		[34]			
		Chronic pulmonary aspergillosis				[44•]
		Pulmonary invasive aspergillosis				[45]

Tanıda Görüntüleme yöntemleri

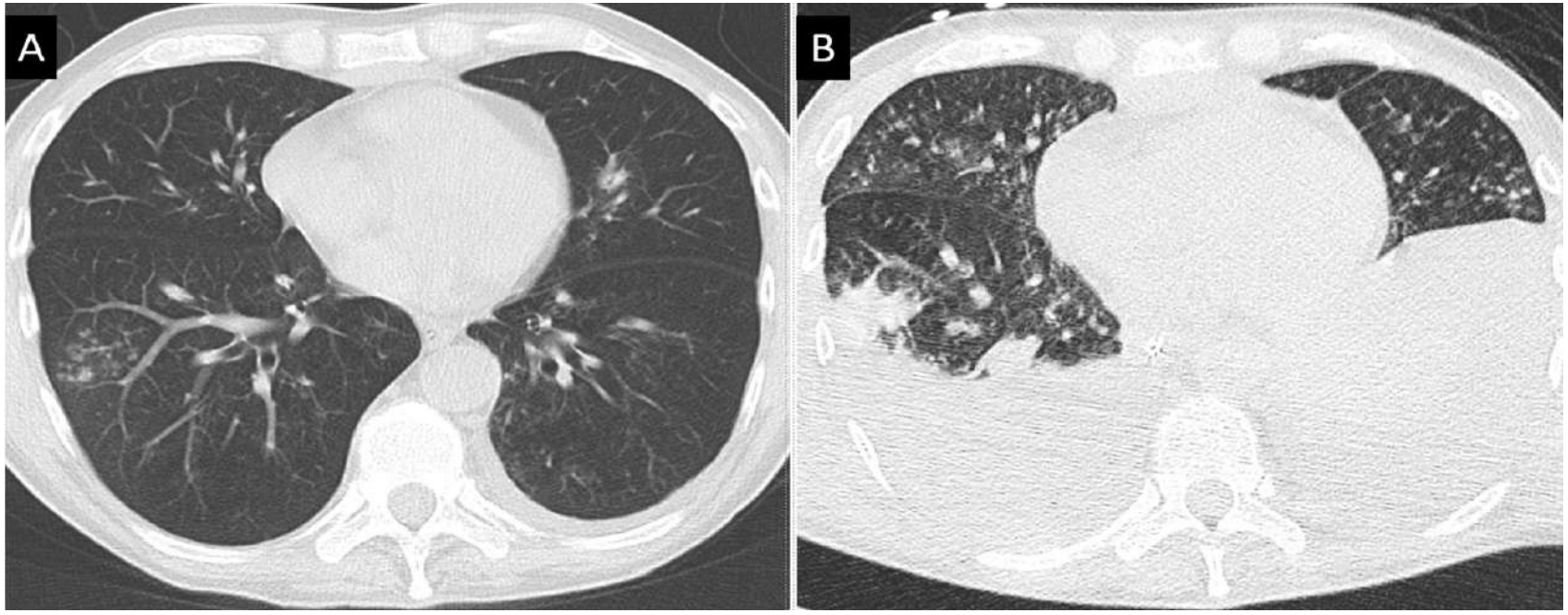
İmmün Duruma Göre Radyolojik Özellikler



Diagnostics 2023, 13, 440



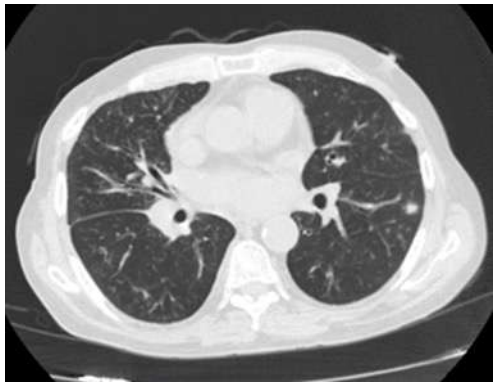
Refrakter AML hastasında IPA;**nötropenik** tanı ve tanıdan 4 hafta sonra

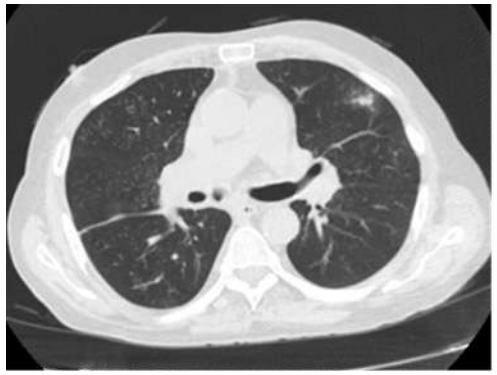


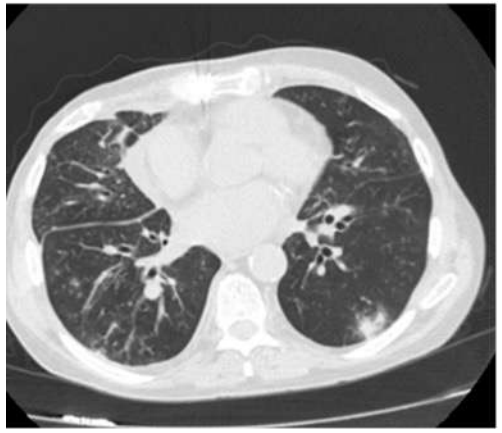
B Cell lenfoma MAB + steroid tx, **nonnötropenik** influenza PCR (+); 2 hafta ara ile CT görüntüleri

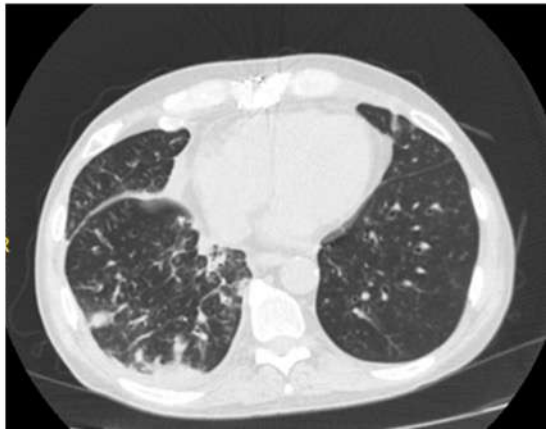
J. Fungi **2023**, *9*, 131

CT









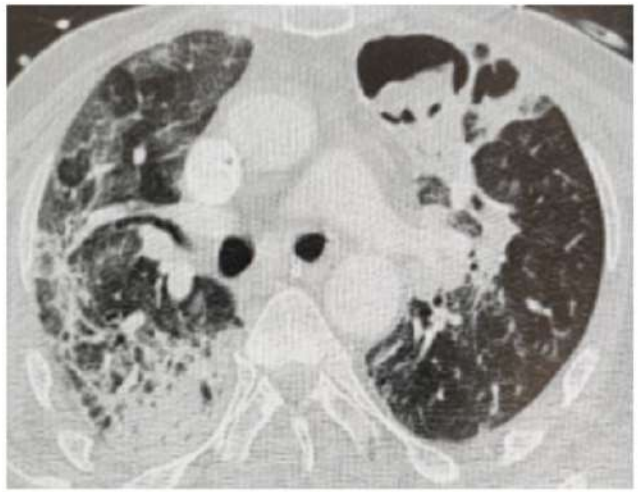
Değişik kesitlerde pulmoner aspergillozis görüntüsü. Bal örneklemesi ile Aspergillus pcr ve kültür pozitif . Bx Aspergillus hif +

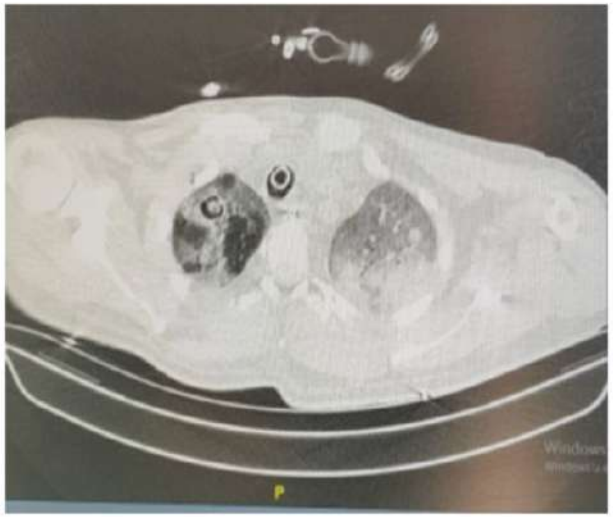
Olguda **nodüler ve konsolidasyon oluşturmaya meyilli birleşen nodüler infiltrasyonlar** izlenmektedir.

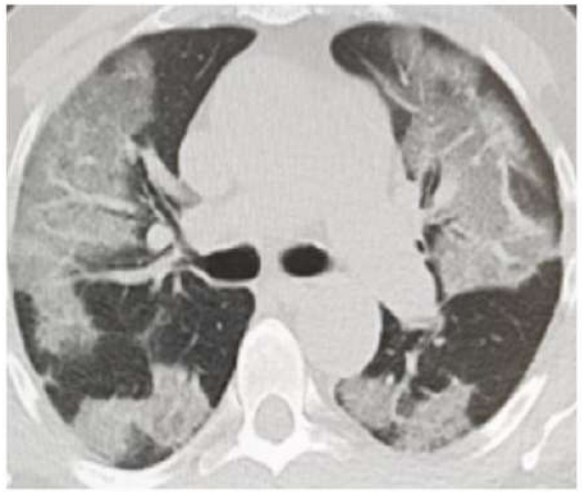
IAPA ve CAPA da Görüntüleme ne kadar etkin?

IAPA ve CAPA gelişen hastalarda radyolojik bulgular genelde non-spesifik, klasik bulgular (nodül, hava-hilal, kavite) nadir

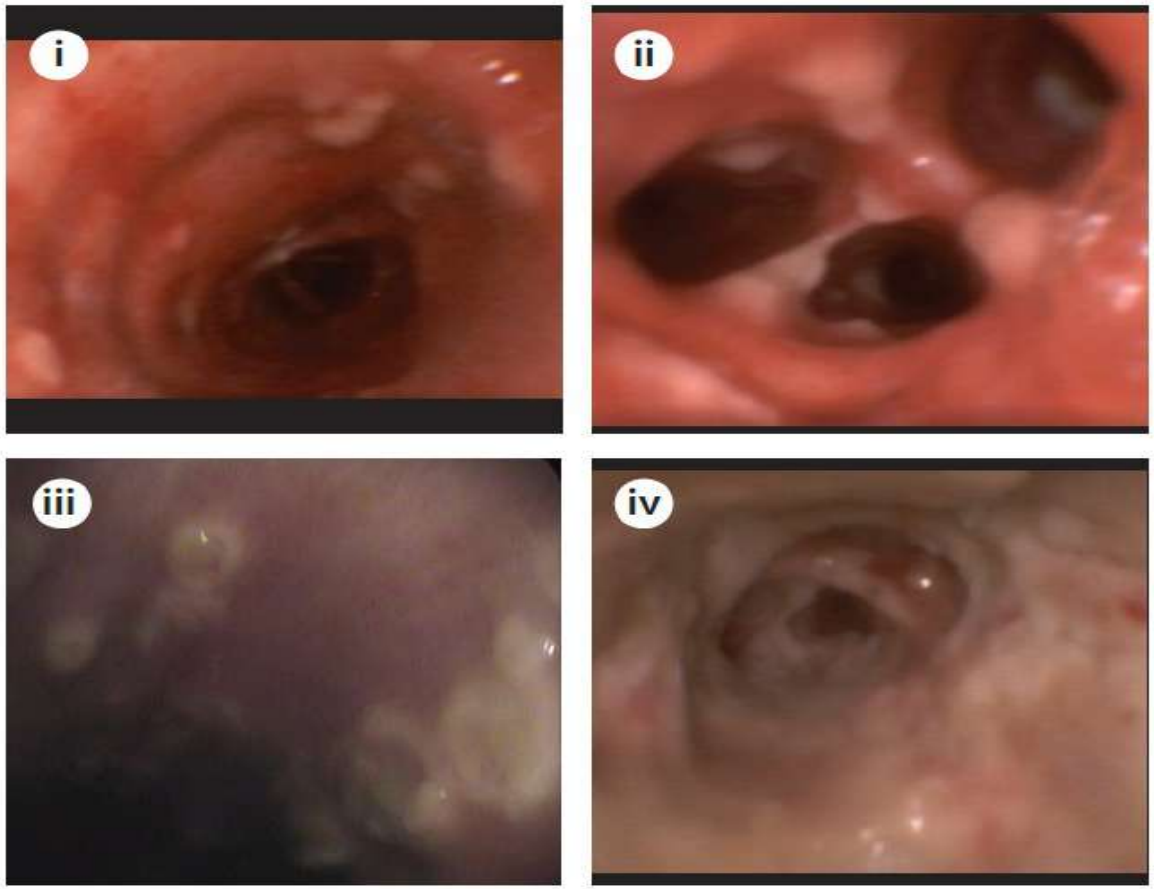
Uygun antibakteriyel tedaviye yanıtsız olgularda ilerleyen pnömonik infiltrasyon İA açısından şüphe uyandırmalı



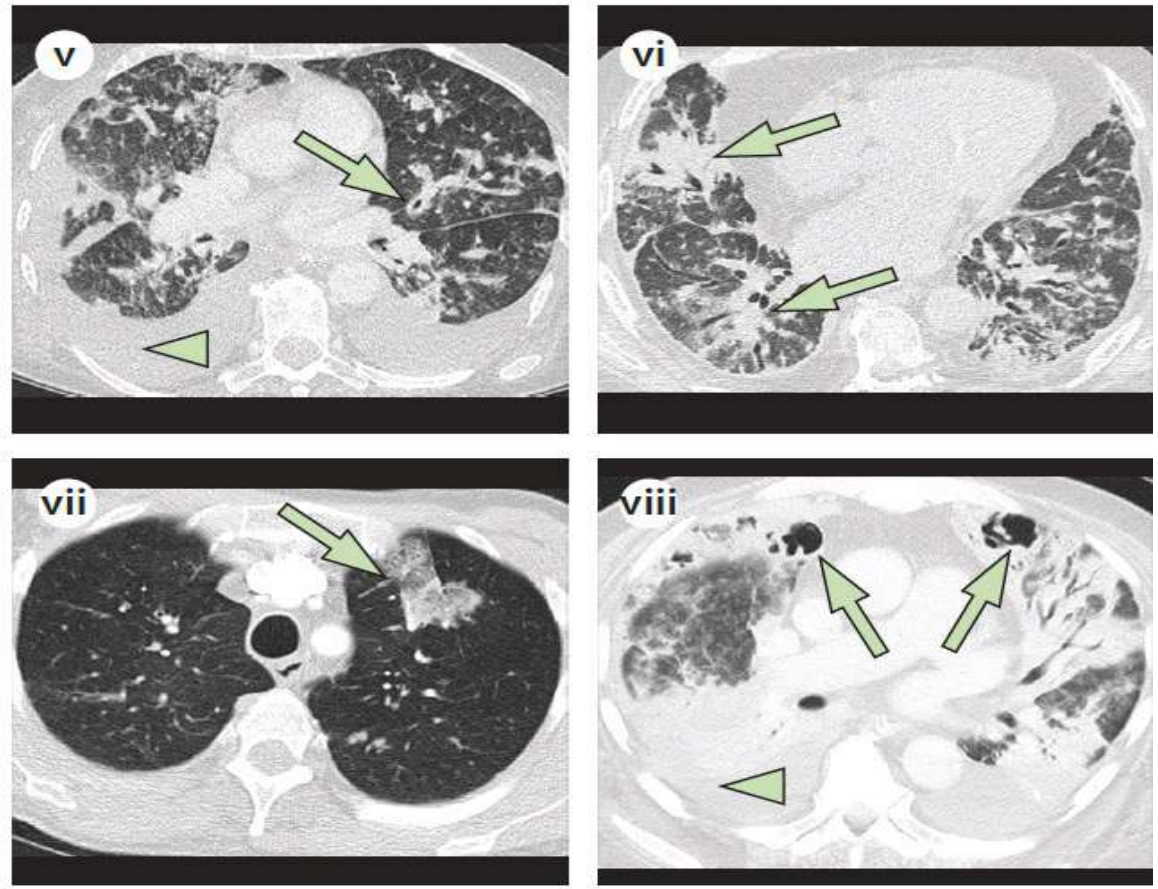


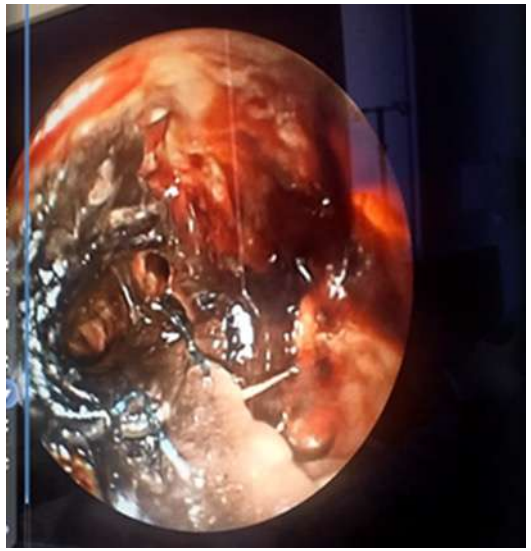


Invasive *Aspergillus* tracheobronchitis

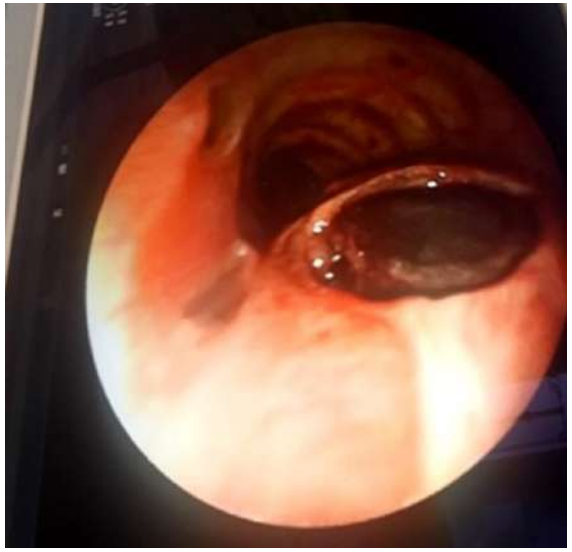


Pulmonary IAPA and CAPA





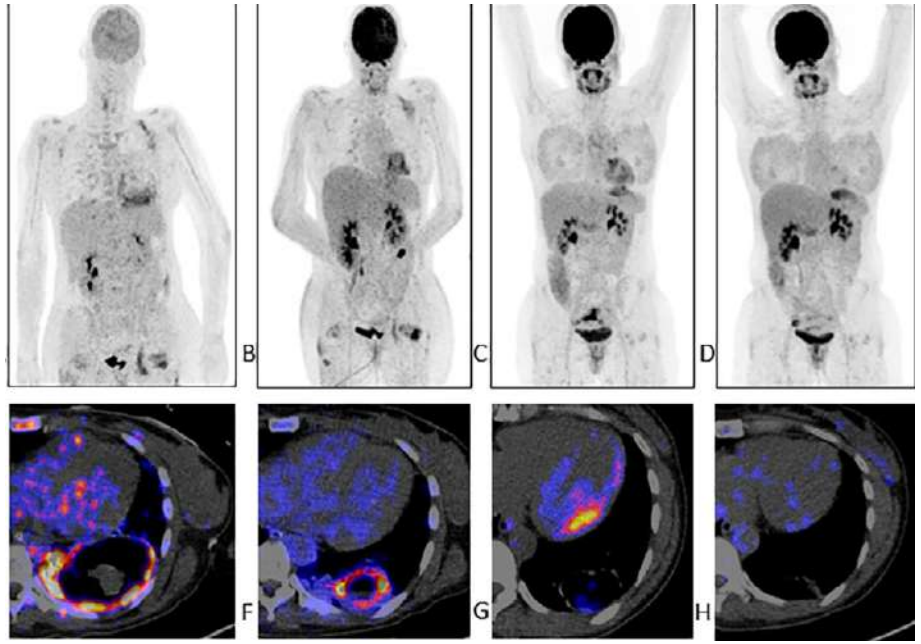
Anostomoz alanını etkileyen bronşiyal aspergillozis.Bronşiyal anostomozda dehisense neden oldu.



Sol ana bronş membranöz yüzde içinde hif saptanan bronşiyal Aspergillus lezyonu

PET/BT

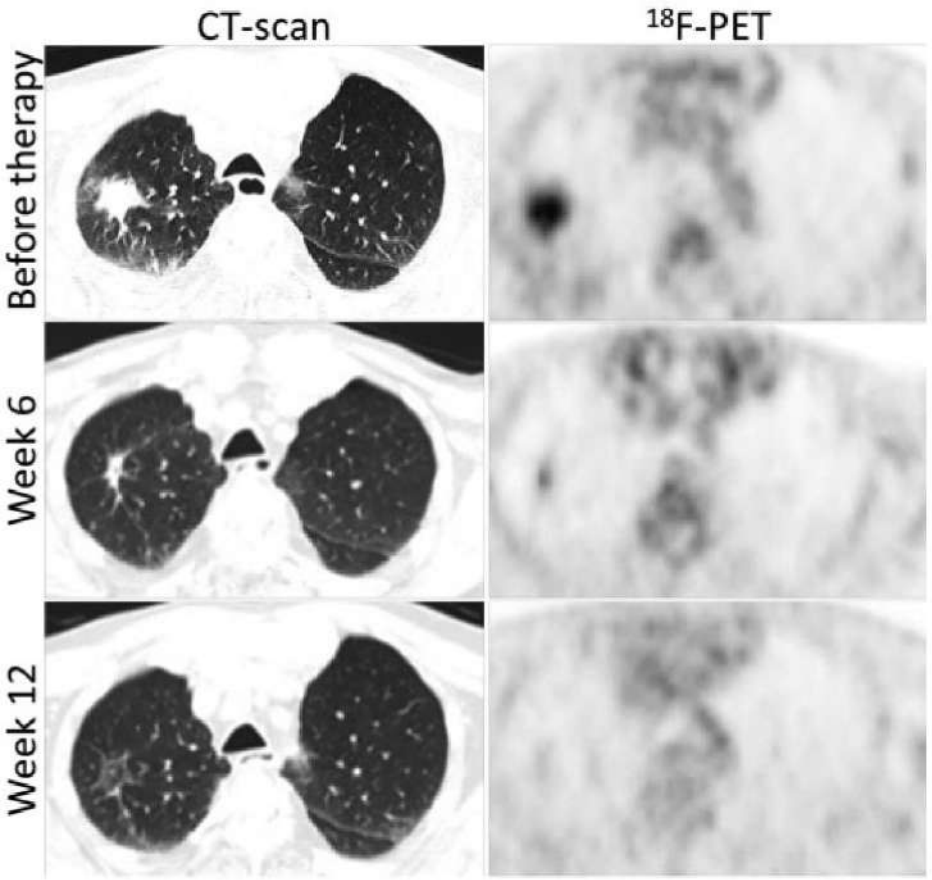
İA'da anatomik ve fonksiyonel bilgi verir!!!



SOT hastasında İPA sonrası göğüs duvarı ve yumuşak doku tutulumları

Pansitopenili AML hastası, solunum sıkıntısı; CT kavite ve aspergilloma; tedavi sonrası PET/CT ile hastalık aktivasyonunun takibi

PET/BT ile hastalık aktivasyonu



Konsolidasyonun ikinci kürü sırasında invazif aspergillozu olan bir AML hastasında BT taraması ve PET taraması.

BAL'da Aspergillus fumigatus pozitif. İlk BT taramasında tipik bir anjiyoinvazif aspergilloz ve bir nodül (ancak kısmen halo işareti ile çevrili) . Nodül hipermetaboliktir (maksSUV ¼9,8),

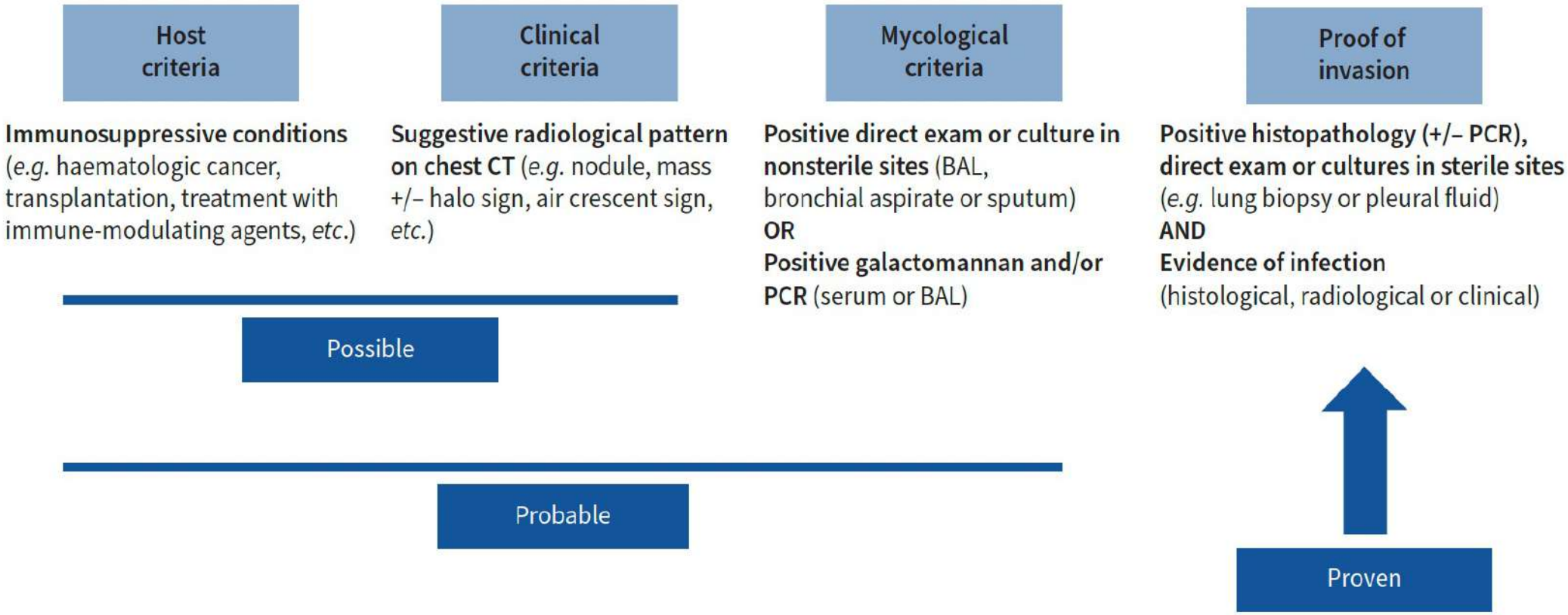
6. haftada nodülün boyutu önemli ölçüde küçülmüş ancak hala hafif hipermetabolik (maksSUV¼2,5).

12. haftada, sadece metabolik aktivitesi olmayan rezidüel bir skar vardır.

Semin Respir Crit Care Med 2020;41:80–98.

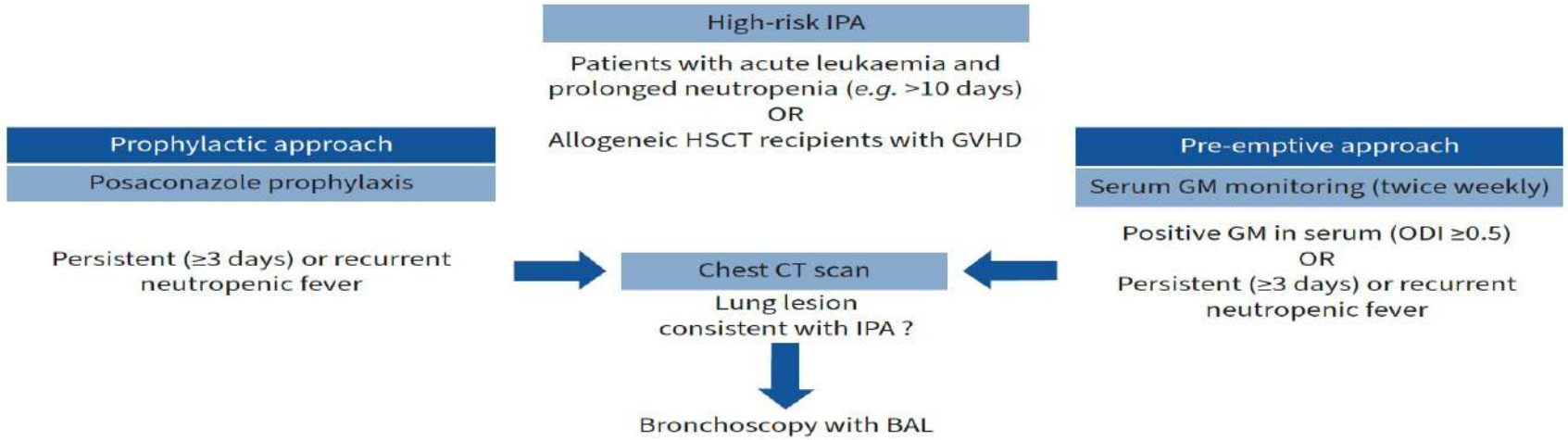
Klinikte Tanıyı Nasıl Koyalım??

EORTC Mantar çalışma Grubu'na göre



Eur Respir Rev 2022; 31: 220114

Yüksek Riskli Hematolojik Malignitelerde İPA Tanısı



IPA diagnosis		**Probable**			**Suspected but not fulfilling EORTC/MSGERC criteria**
Serum GM	Negative	Negative	Positive	Positive	Positive
Chest CT	Positive	Positive	Positive	Positive	Negative
	Negative or not performed	Positive	Negative or not performed	Positive	Not performed
Intervention	AF therapy Reassess (follow-up CT) +/– Biopsy of lesion	AF therapy			Repeat serum GM Extrapulmonary IA? (brain MRI, abdominal CT)

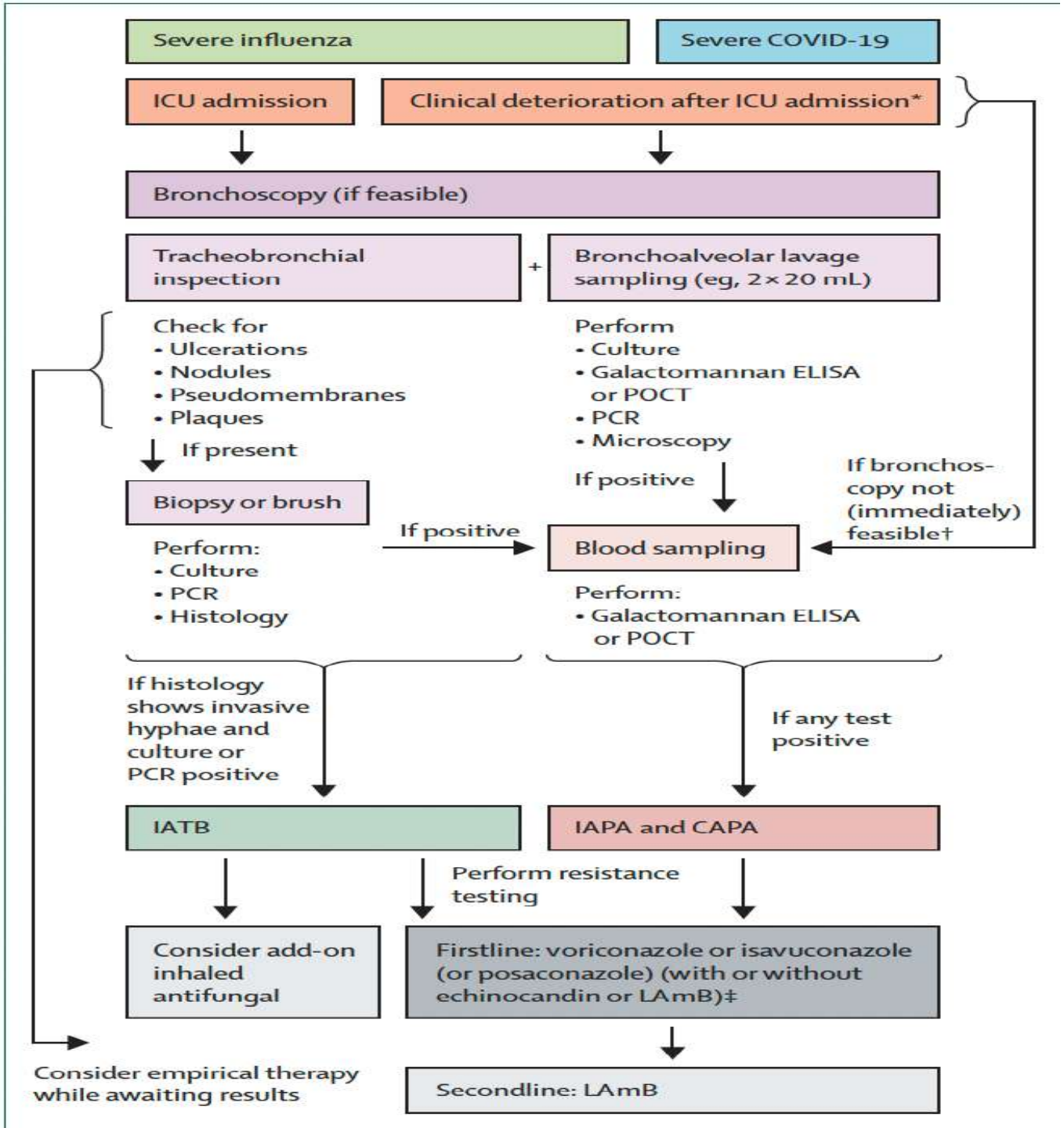
Eur Respir Rev 2022; 31: 220114

Influenza-associated and COVID-19-associated pulmonary aspergillosis in critically ill patients

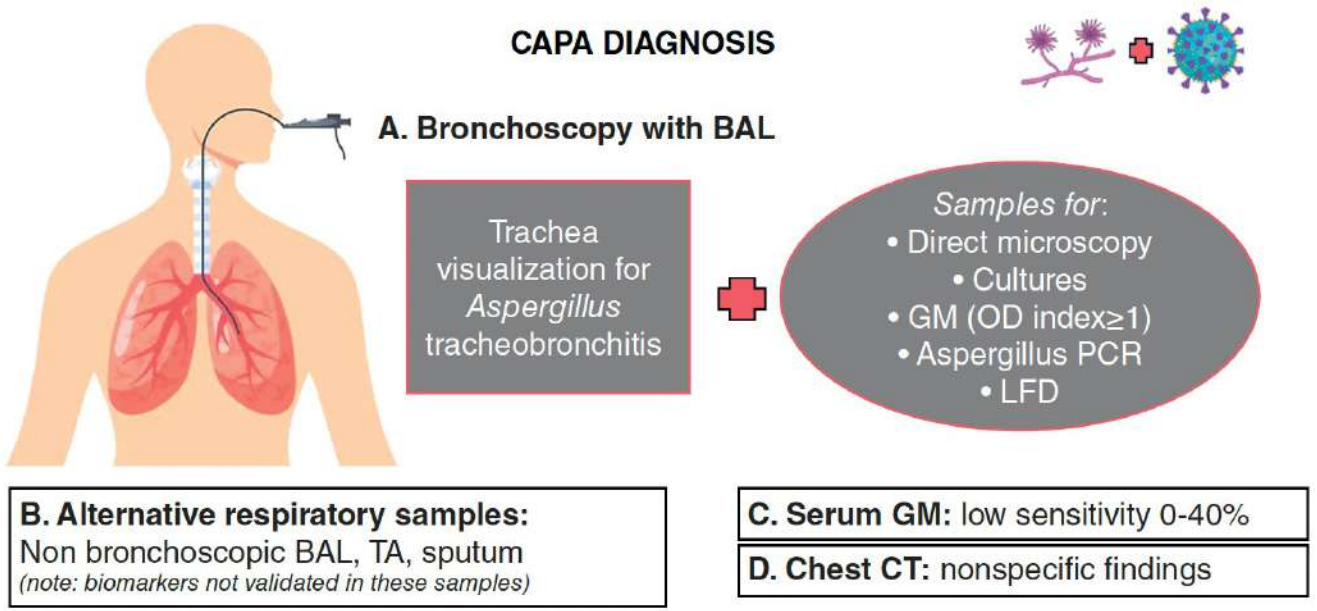
Simon Feys, Agostinho Carvalho, Cornelius J Clancy, Jean-Pierre Gangneux, Martin Hoenigl, Katrien Lagrou, Bart J A Rijnders, Laura Seldeslachts, Lore Vanderbeke, Frank L van de Veerdonk, Paul E Verweij, Joost Wauters

Lancet Respir Med 2024;

Influenza-associated pulmonary aspergillosis (IAPA) and COVID-19-associated pulmonary aspergillosis (CAPA) are



CAPA tanısı


CAPA DIAGNOSIS
A. Bronchoscopy with BAL
Trachea visualization for *Aspergillus* tracheobronchitis
Samples for:
• Direct microscopy
• Cultures
• GM (OD index≥1)
• Aspergillus PCR
• LFD
B. Alternative respiratory samples:
Non bronchoscopic BAL, TA, sputum
(note: biomarkers not validated in these samples)
C. Serum GM: low sensitivity 0-40%
D. Chest CT: nonspecific findings

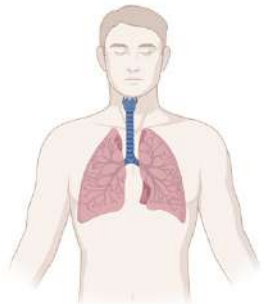
Mycopathologia (2024) 189:69
https://doi.org/10.1007/s11046-024-00879-6

OPINION ARTICLE

Optimizing Antifungal Treatment Strategies to Prevent Invasive Pulmonary Aspergillosis Infection-Related Deaths in Intensive Care Unit Patients: The Need for Standardization of Research Definitions

Matteo Bassetti · Antonio Vena · Martina Bavastro · Daniele Roberto Giacobbe

Assessment of ICU patients with suspected IPA for research inclusion



Research definitions have been develop to maximize specificity, with some losses in sensitivity that are acceptable for research purposes but that should not be taken as an absolute rule also for treatment decisions in clinical practice

More limited spectrum of host factors (e.g., FUNDICU definitions)

- Influenza
- COVID-19
- Moderate/severe COPD
- Decompensated cirrhosis
- Uncontrolled HIV infection
- Solid tumors

Practical considerations

- Possibly different (higher) cut-off of acceptable loss in sensitivity compared with clinical practice

Strenght

- Aimed at high specificity (to improve comparability and generalizability of research findings)

Limitation

- Still based on "probable" category and not on more precise calculation of probability

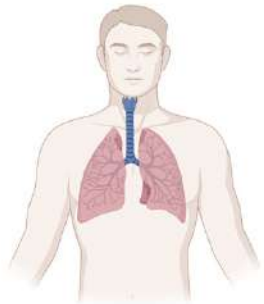
Mycology (e.g., FUNDICU)

- BAL cultures
- Serum GM
- BAL GM

CT scan

- Frequently aspecific findings (differential diagnosis with bacterial infections, that could also be concomitant)

Assessment of ICU patients with suspected IPA for treatment purposes



In selected situations, antifungal treatment could be considered in patients not fulfilling IPA research definitions but showing possible risk factors, positive mycological tests and radiology findings, in the absence of alternative diagnoses

Broad risk factors identified in the literature

- Malignancy
- COPD
- Influenza
- COVID-19
- Systemic steroids (either long or short term)
- Inhaled steroids
- Liver cirrhosis
- Organ transplantation
- AIDS
- Malnutrition
- Transfusions
- Sepsis/MOF
- Immunosuppression for systemic diseases
- Severe burns
- Post-cardiac surgery status
- Prolonged ICU stay
- Non-fungal pneumonia
- Antibiotics
- Alcoholism
- CGD
- Hemodialysis
- Congestive heart failure
- Near-drowning
- Invasive procedures
- Diabetes mellitus
- Severe bacterial infection
- Smoking
- Concentration of *Aspergillus* spores in the air
- Surgery
- Immunoparalysis

Mycology

- URTI and LRTI cultures
- Serum fungal antigens
- BAL fungal antigens
- Non-BAL fungal antigens
- Respiratory PCR

Teşekkürler...