İNVAZİF ASPERGİLLOZ

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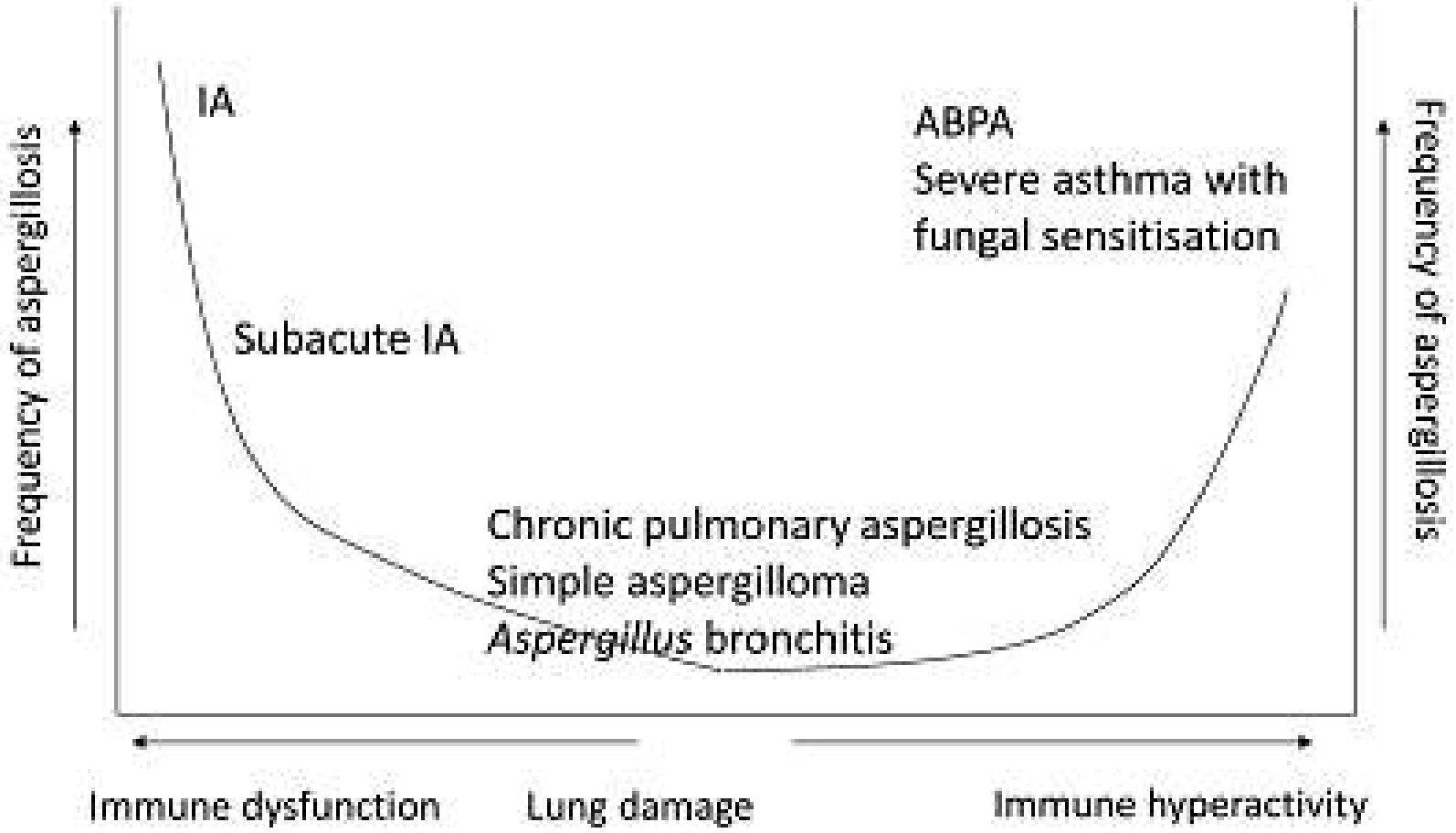
Aspergilloz

- Allerji
- Havayolu veya akciğer invazyonu
- Kutanöz enfeksiyon
- Akciğer dışı

- *A. Fumigatus*;en sık
- *A. Flavus; en allerjik*
- *A. Terreus;en dirençli*



Kosmidis C, Denning DW. *Postgrad Med J* 2015;**91**:403–410. doi:10.1136/postgradmedj-2014-206291rep

Risk Faktörleri

- Nötropeni!!!
- Trombositopeni!!!
- CMV enfeksiyonu

Nötropenik Konak

- Kortikosteroid kullanımı
- Solid organ transplantasyon
- AIDS
- KOAH
- YBÜ hastaları
- Karaciğer Yetmezliği
- Uzun süreli diyaliz
- Kronik Granulomatöz Hastalık
- Kolonize kistik fibroz

Akciğer!!!

Non-nötropenik konak

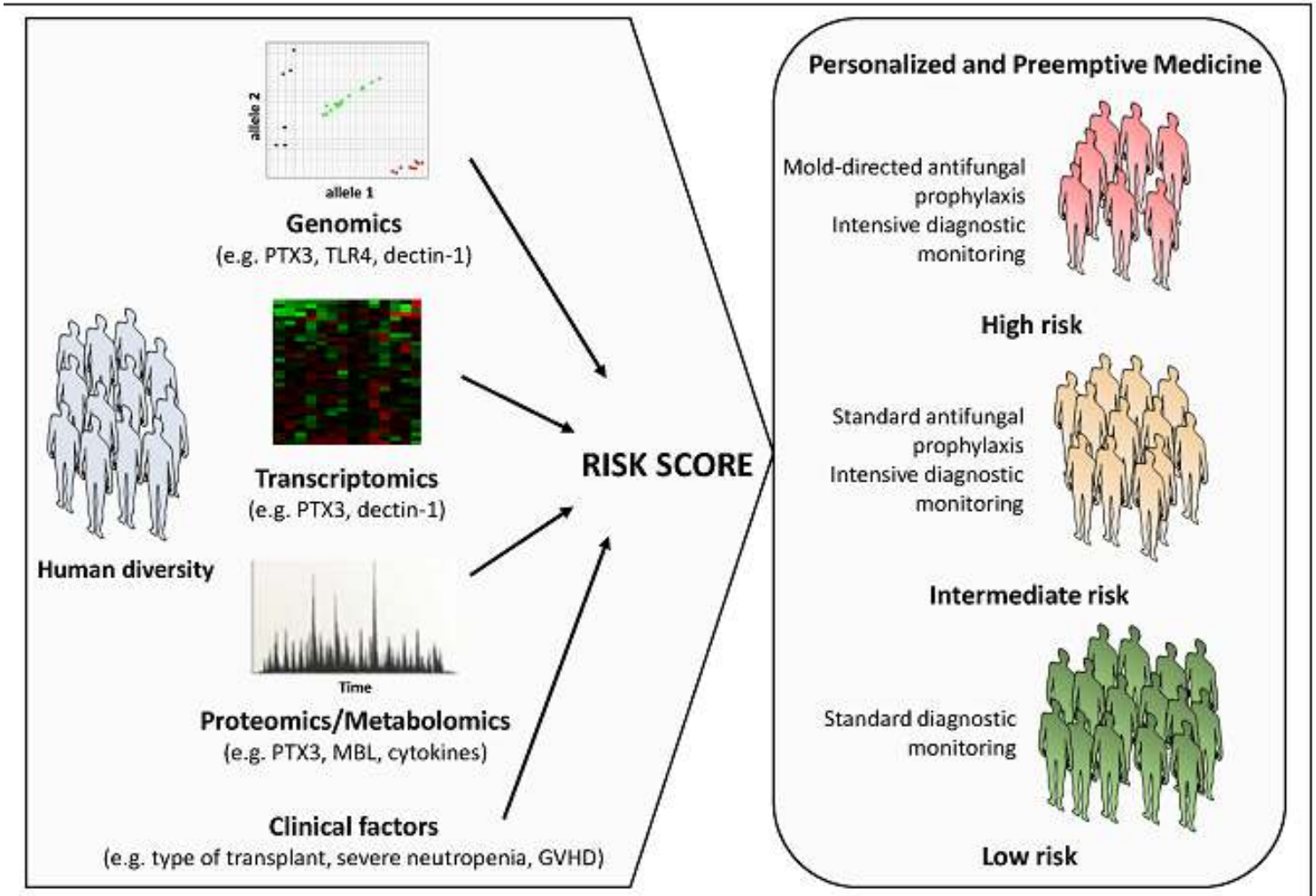
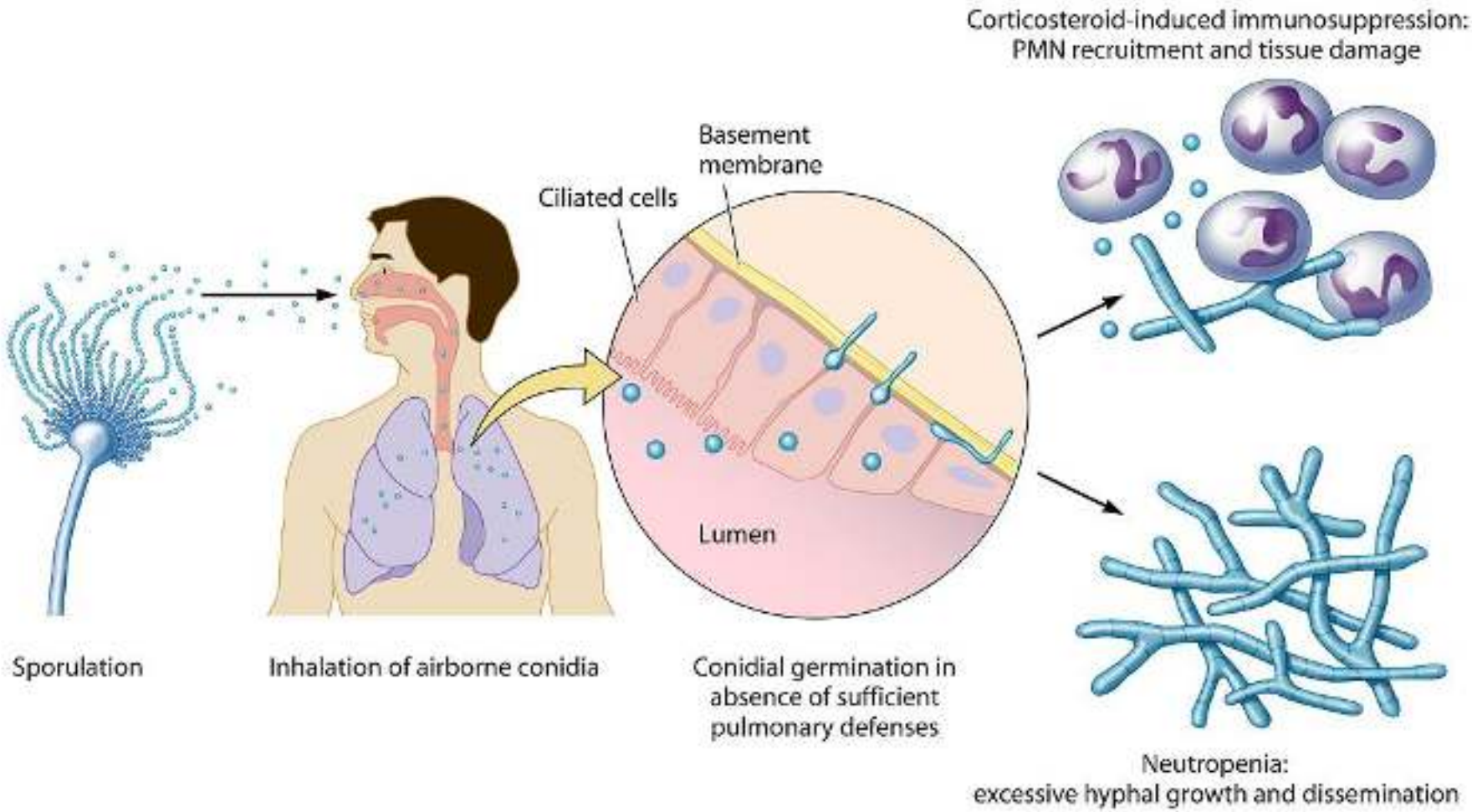


FIGURE 1 | Schematic representation of a personalized medicine approach to the management of IA. A prognostic score calculated using information on host biomarkers and clinical factors is used to determine the risk of IA associated to a given patient profile. The individual aspects of the patient (and donor), including the genetic make-up and downstream activated transcriptomic and proteomic or metabolomic networks, as well as inherent clinical factors are directly considered to guide treatment planning. Although the risk category is defined at initiation of treatment (or before stem cell transplantation), it may be updated in the course of treatment according to the clinical status of the patient (e.g., development of graft-versus-host-disease, prolonged neutropenia, etc.). A number of host genetic variants in innate immunity genes (e.g., PTX3, TLR4, dectin-1, MBL, and several cytokines) have been disclosed as promising targets to use in patient-tailored strategies to optimize and target the diagnostic workup, and the antifungal prophylaxis and therapy, thereby improving patient outcome.



conidial clearance, production of inflammation, and killing of invasive forms

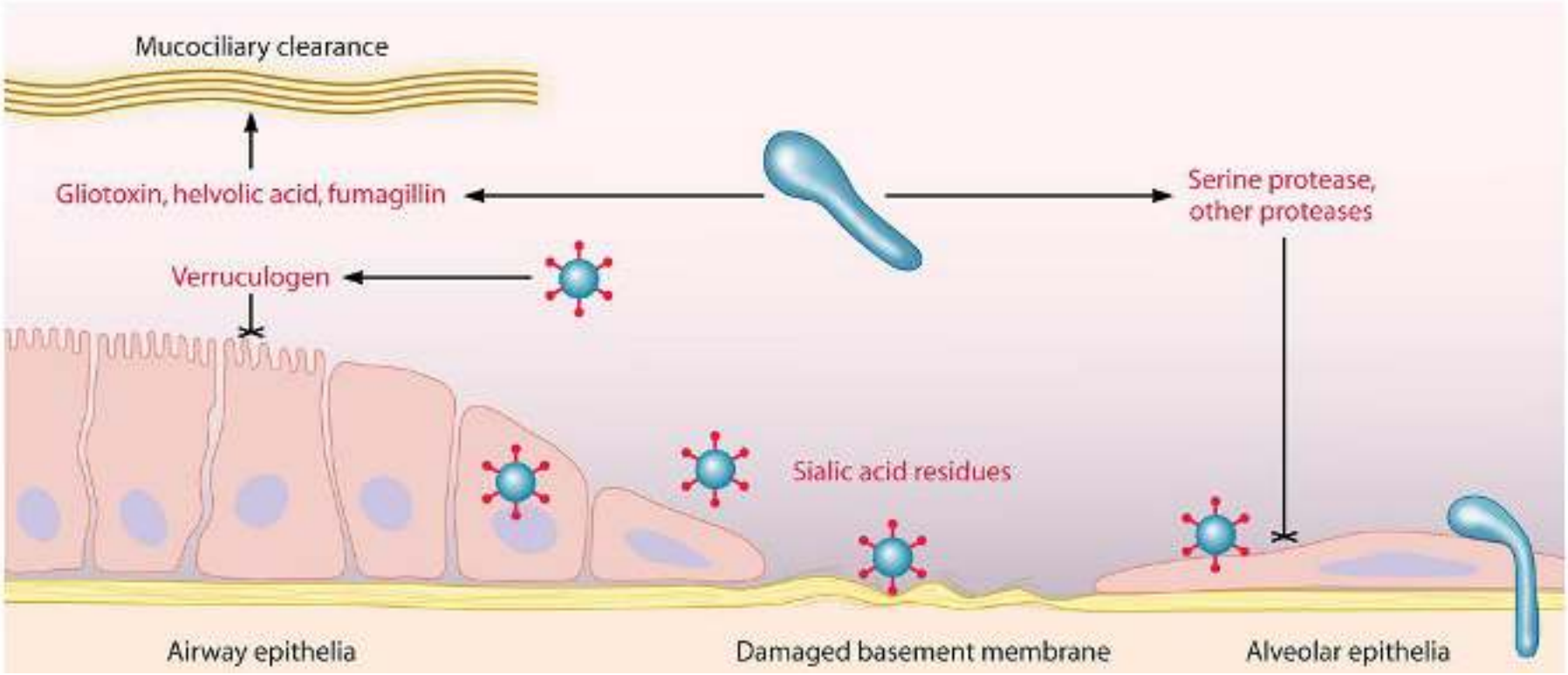


FIG. 2. Interaction of *A. fumigatus* with respiratory epithelia. Following inhalation, *A. fumigatus* encounters airway epithelia (lining trachea, bronchi, and bronchioles), the mucus and fluid lining the upper respiratory tract, and, ultimately, the alveolar space. Fungal products (shown in red) may enhance colonization through tissue injury (cross-haired line) and attachment to epithelial cells or damaged basement membrane. Conidia may also germinate and invade the surrounding lung tissue via the basement membrane or following ingestion by epithelial cells.

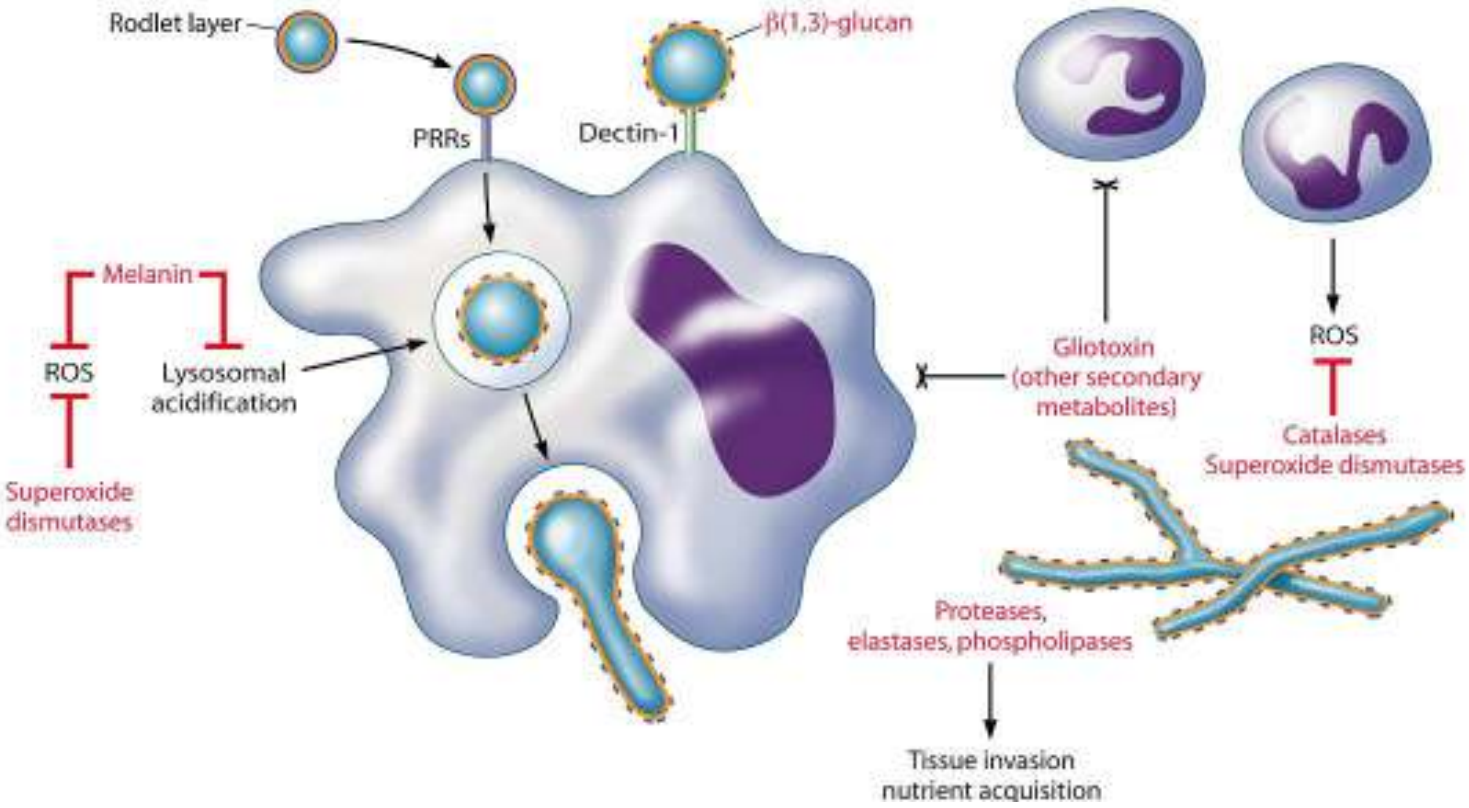


FIG. 3. *A. fumigatus* interactions with phagocytes. Alveolar macrophages phagocytose inhaled conidia via PRRs. Conidial swelling (within or outside of the macrophage) releases the protective rodlet layer, exposing β(1,3)-glucan for recognition by dectin-1. Dectin-1–β(1,3)-glucan interactions are primarily responsible for the activation of macrophage proinflammatory responses, including conidial killing. Neutrophils attach to hyphae and degranulate, damaging hyphae by oxidative and nonoxidative mechanisms. Neutrophils may also aggregate conidia and prevent germination. Compromised phagocyte function is the primary risk factor for IA. Fungal products (shown in red) may contribute to fungal pathogenicity in these immunocompromised hosts by evading or modulating host defenses.

ASPERGİLLOZ

Aspergillusa hava yolu maruziyeti

Kolonisazyon
Hastalıksız süreç

Invaziv aspergilloz
- Akut (<1 ay)
- Subakut/kronik necrotizan (1-3 ay)

kronik aspergilloz (>3 ay)
- Kronik Kaviter pulmoner
- Aspergilloma
- Kronik fibrozan pulmoner
- Kronik invaziv sinuzit
- sinus aspergilloması

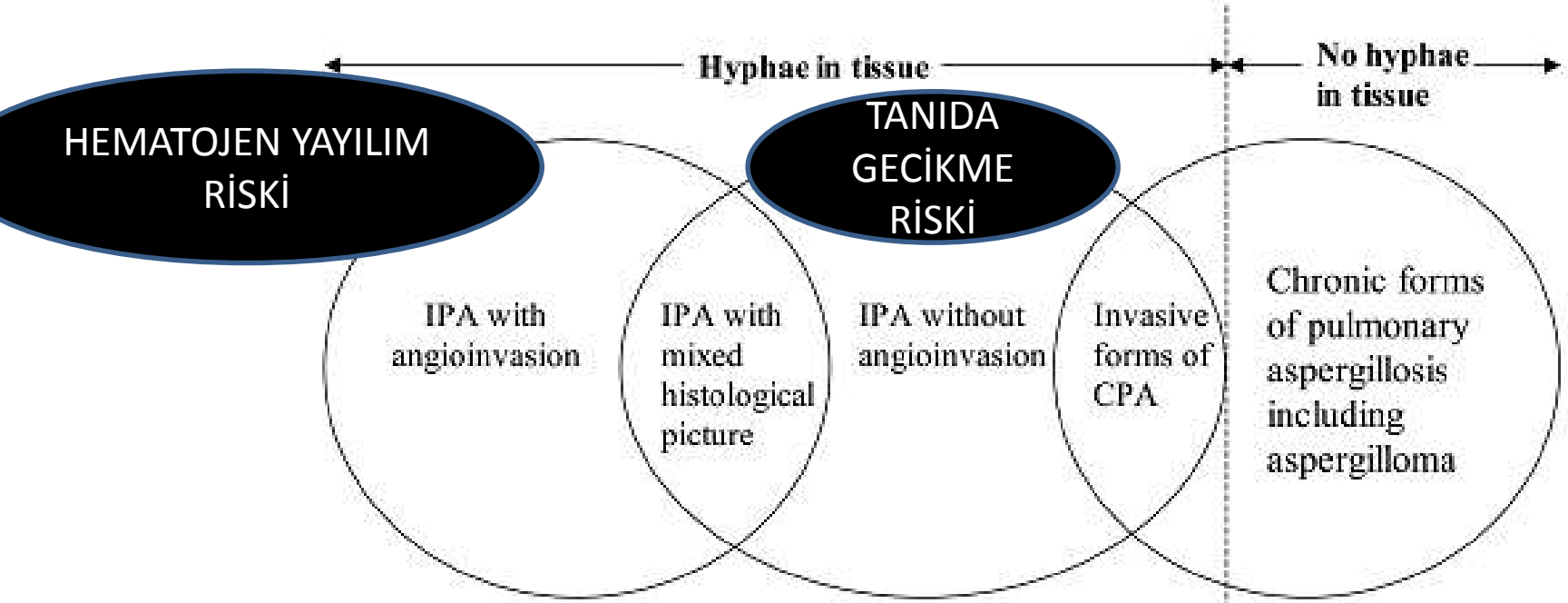
Allerjik
- Allerjik bronkopulmoner (ABPA)
- Extrinsik allerjik (bronko) alveolitis (EAA)
- Astım benzeri klinik
- Eozinofilik rinosinuzit

KLİNİK

- Ateş
- Plöritik ağrı
- Hemoptizi

- Klinik bulgu vermeyebilir !!!!
- Postmortem tanı!!!

KLİNİK

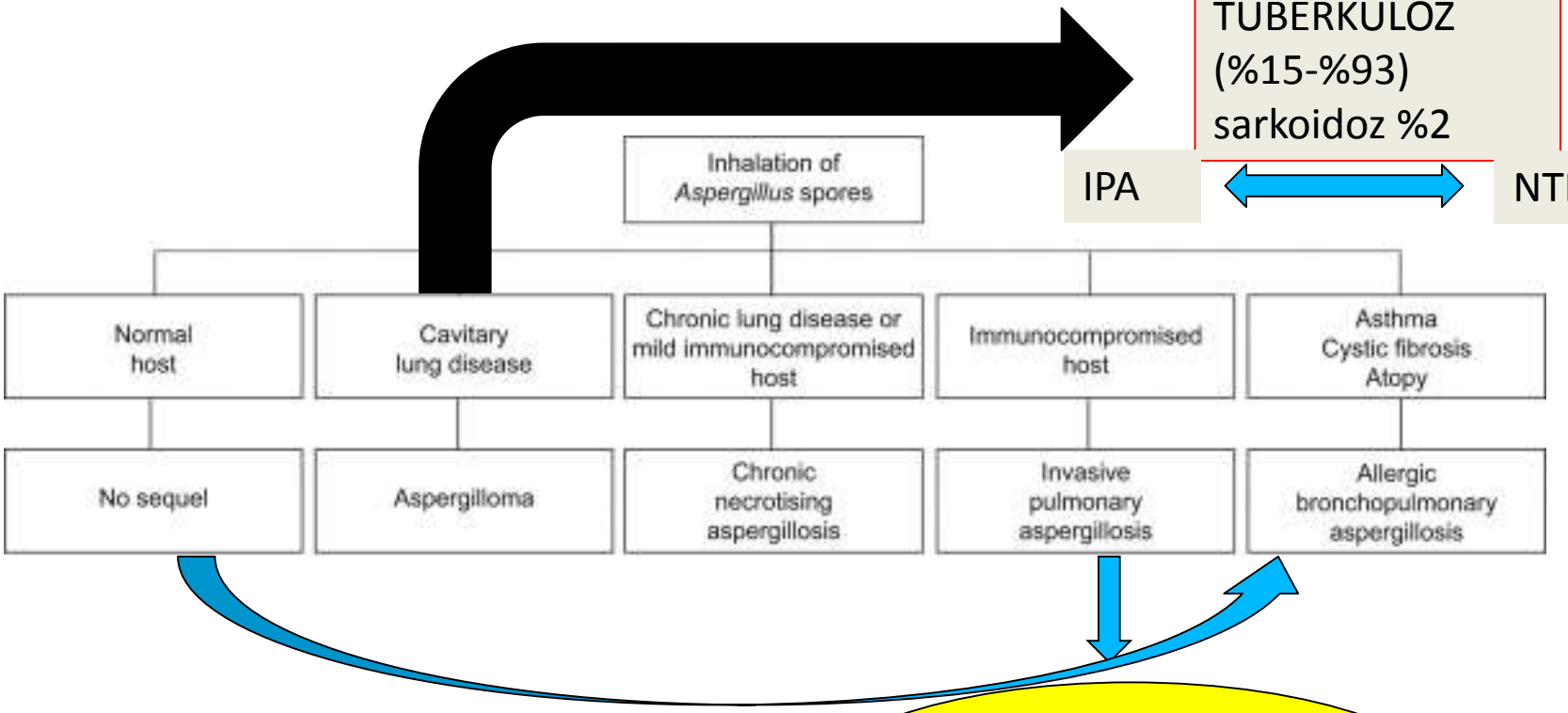


Pathology	Angioinvasion, coagulative necrosis, haemorrhagic infarction	No angioinvasion, pyogranulomatous inflammation, inflammatory necrosis	No angioinvasion, hyphae confined to pre-existing lung cavity
Host	Prolonged and profound neutropenia	Non-neutropenic with CGD, corticosteroid therapy, HIV/AIDS,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

KLİNİK

TÜBERKÜLOZ
(%15-%93)
sarkoidoz %2

IPA ⟷ NTM



Bronkopnomoni
Trakeobronşit

M. Kousha et al. Eur Respir Rev 2011;20:156-174

AC TRANSPLANT. DİKKAT!!!

KLİNİK

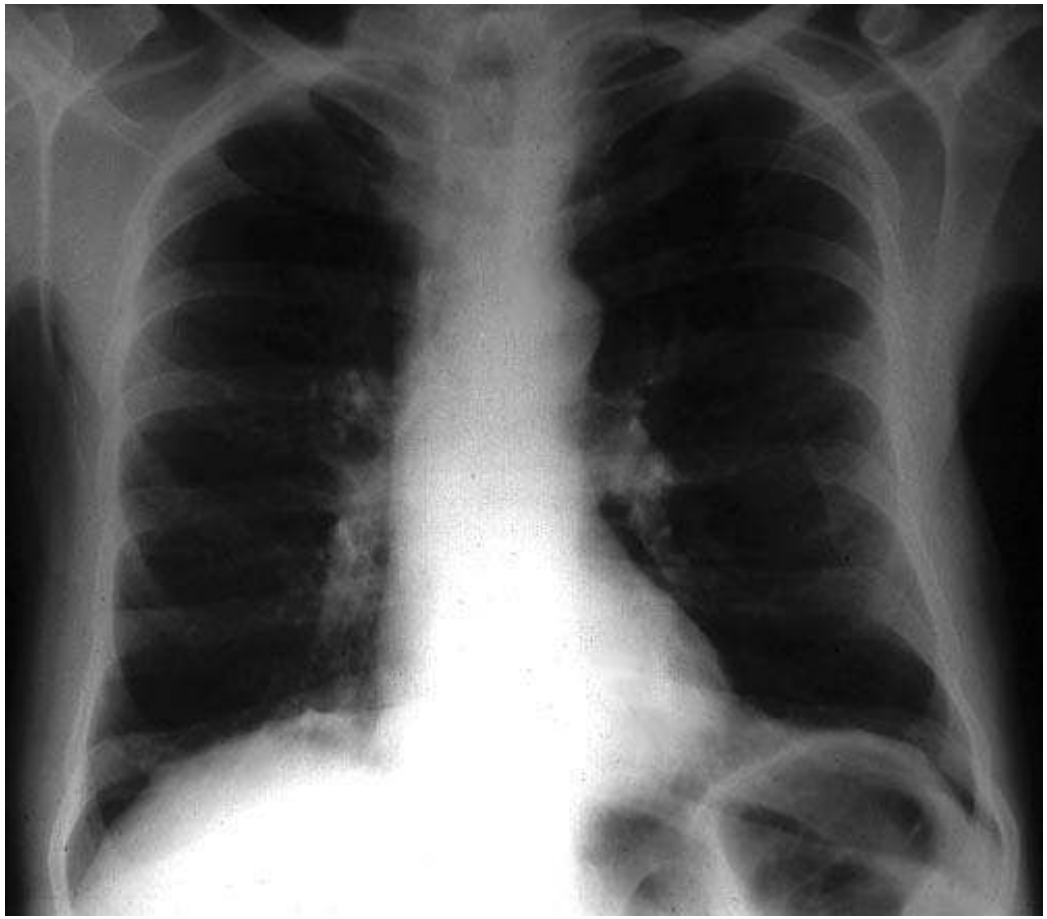
Trakeobronşit

- Tıkayıcı bronşiyal asp.
- Ülseratif
- Psödomembranöz

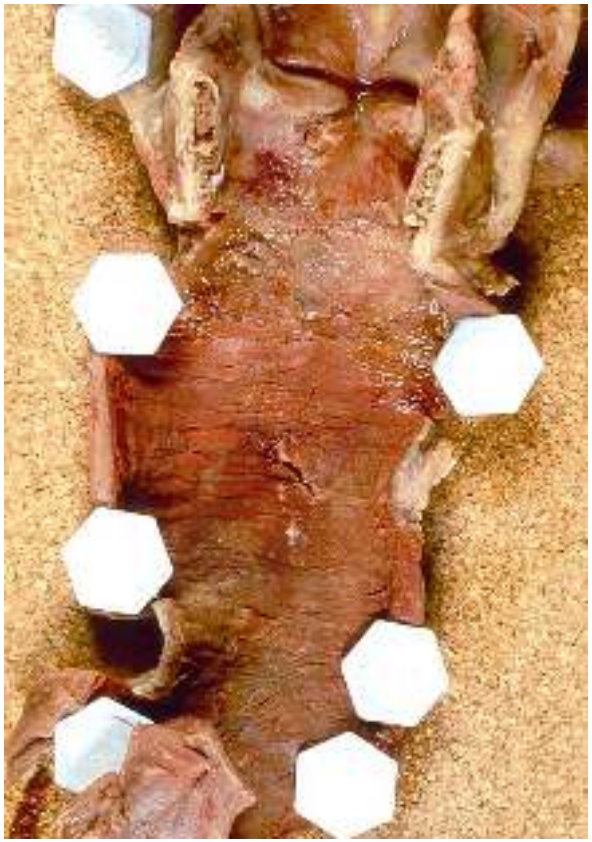
- Özellikle Akciğer transplantlarında

- Görüntüleme; normal, hava yolu kalınlaşması, yama tarzı tutulum,konsolidasyon veya sentrilobuler nodül tarzında olabilir.

Pseudomembranous *Aspergillus* trakeobronşit

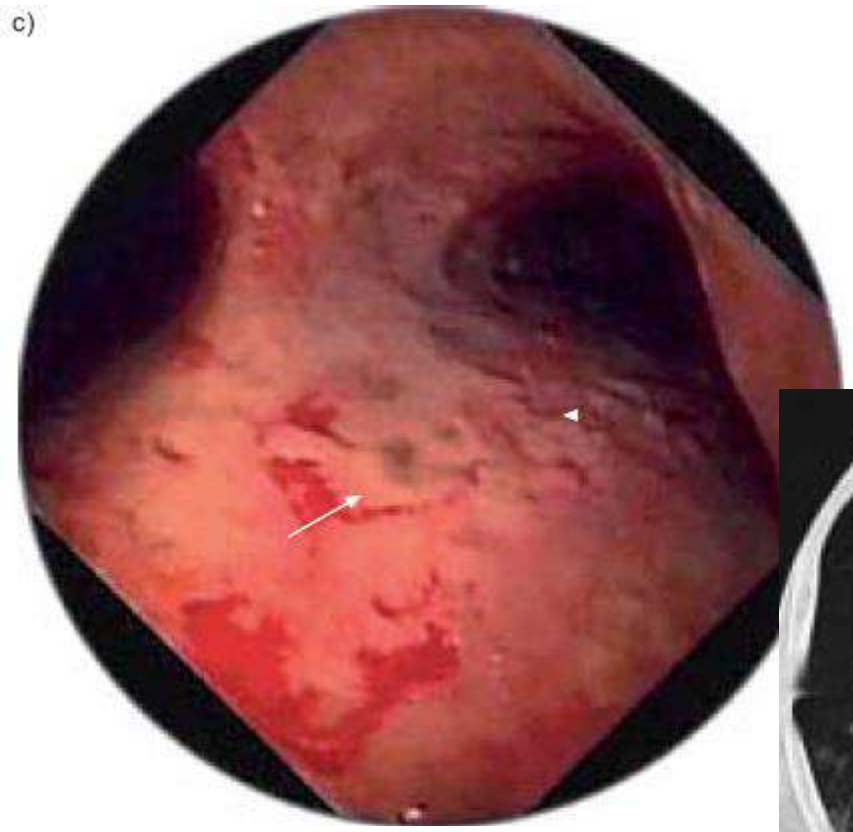


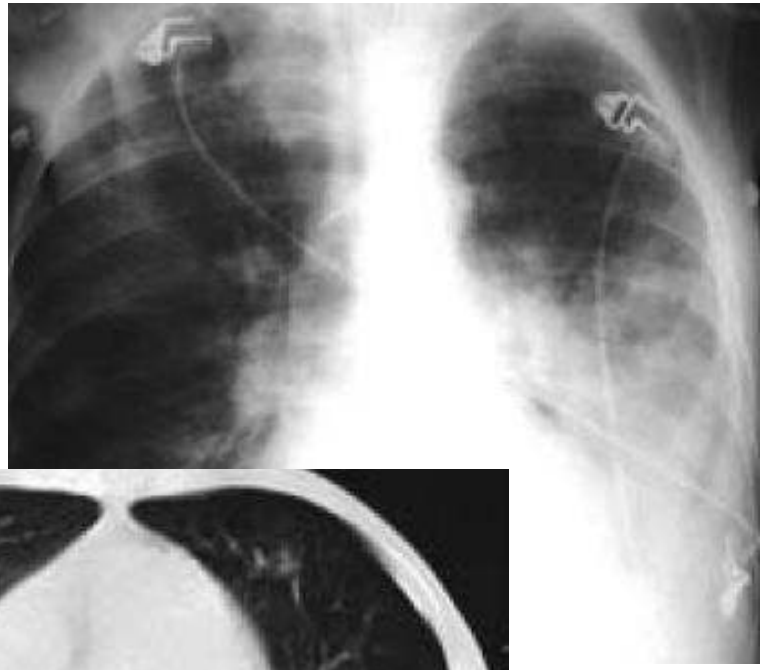
Ciddi wheezing ile başvuran immundüşkün hasta



Tait, Thorax 1993;48: 1285

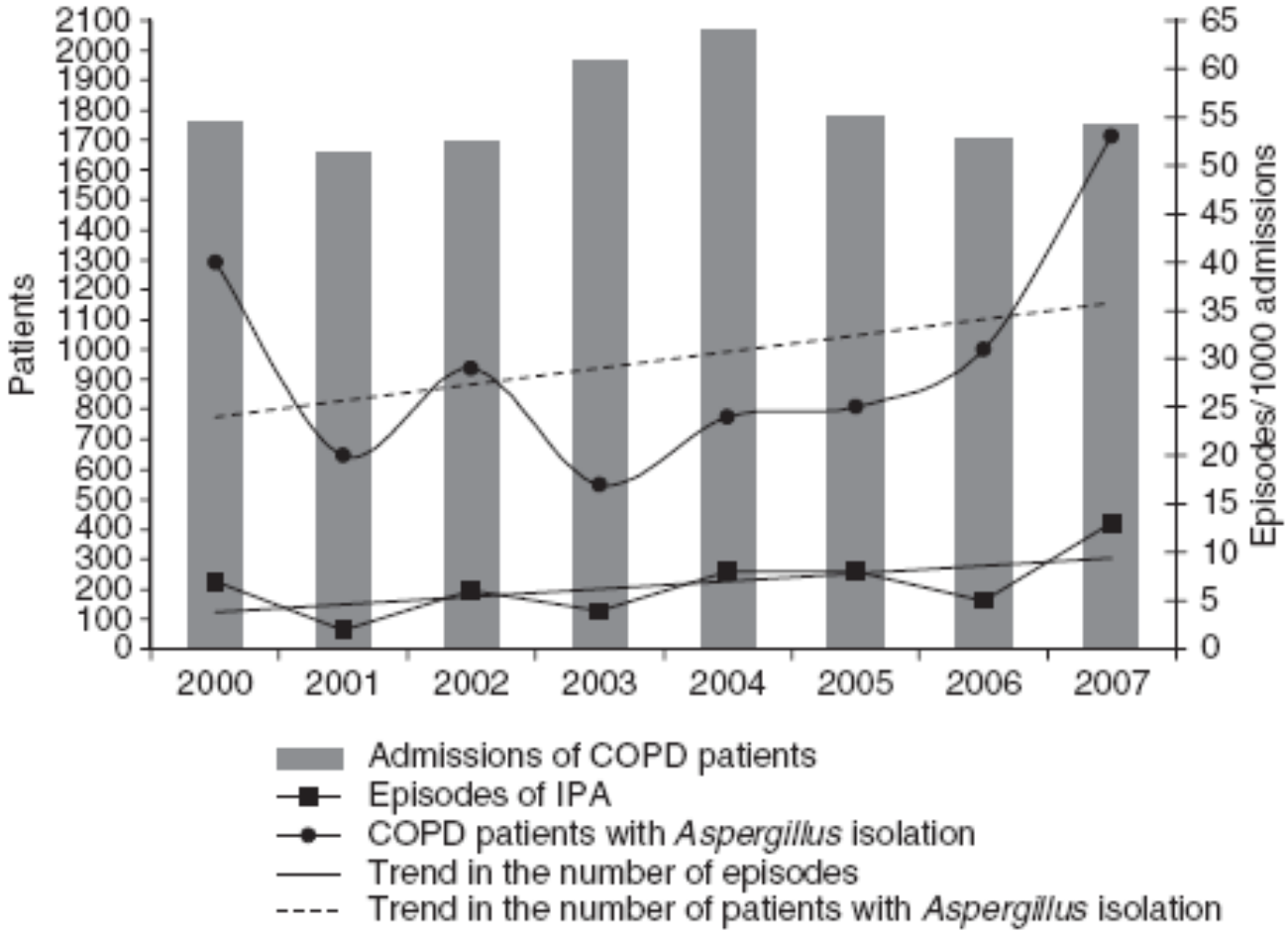
Pseudomembranous *Aspergillus* trakeobronşit + IPA (KOAH hastasında)





Bulpa Eur Resp J 2007;30:782

Aspergillus, IPA and KOAH



~ 22% of *Aspergillus* in KOAH = invasive aspergillosis

Guinea et al, Clin Microbiol Infect 2010;16:870

Aspergillus, IPA VE KOAH

	Wald	p	OR
ICU admission	4.758	0.029	2.406
Chronic heart failure	3.649	0.056	2.102
Accumulated dose of corticosteroids prior to admission[a]	6.213	0.013	2.987
Accumulated dose of corticosteroids during admission[b]	13.338	0.000	4.568
Antibiotic treatment[a]	5.924	0.015	2.570
Constant	66.327	0.000	0.034

ICU, intensive-care unit.
[a]In the 3 months prior to admission.
[b]From admission to the first clinical isolation of *Aspergillus* from LRT samples.

Guinea et al, Clin Microbiol Infect 2010;16:870

Aspergillus, IPA VE KOAH

IA Tanısı için ipuçları

- GOLD Evre 3 veya 4.
- Ciddi wheezing (tracheobronşit)
- Artan infiltrasyon (66%)
- Bilateral infiltrasyon (55%)
- Aspergillus üremesi
- Yüksek doz steroid maruziyeti

Guinea et al, Clin Microbiol Infect 2010;16:870

Invasive aspergillosis in ICU

1850 ardışık YBÜ yatışında 127 (%6.9) hastada aspergillus üremesi tespit edilmiş.

89/127 (%70) hematolojik malignite saptanmadı

67/89 kanıtlı/yüksek olası IA, 33 of 67 (50%) KOAH

Meersemann et al, Am J Resp Med Crit Care 2004;170:621.

İnvazif Aspergilloz - Mortalite

ABD, 23 transplant merkezi

2001-2005, kanıtlanmış ya da yüksek olasılıklı İA

12 haftalık toplam mortalite

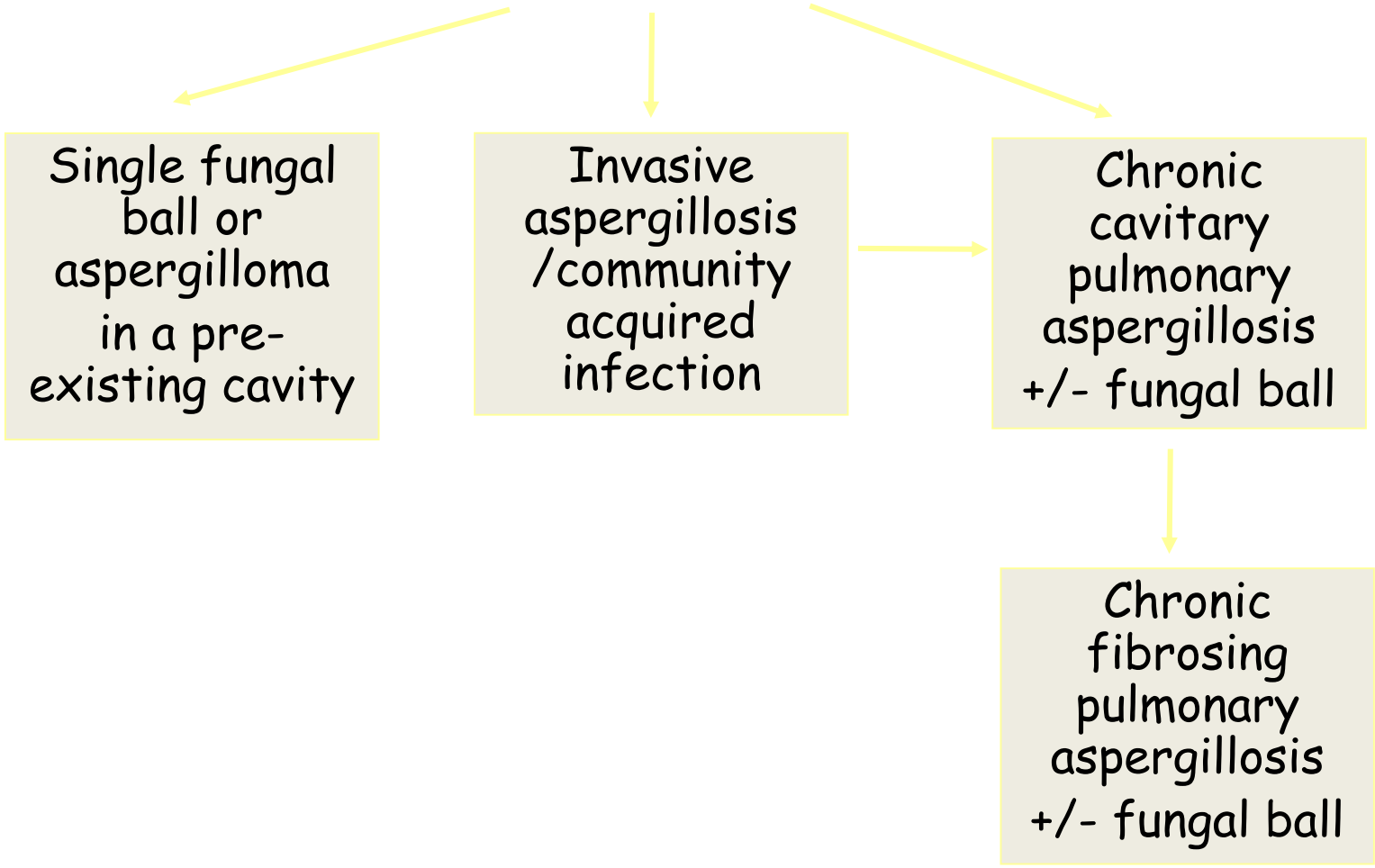
Mortalite: 317/642(%49.4)

Mortalite: HKHT(%57.5) > SOT(%34.4),$p<0.001$

Baddley JW et al. Clin Infect Dis 2010

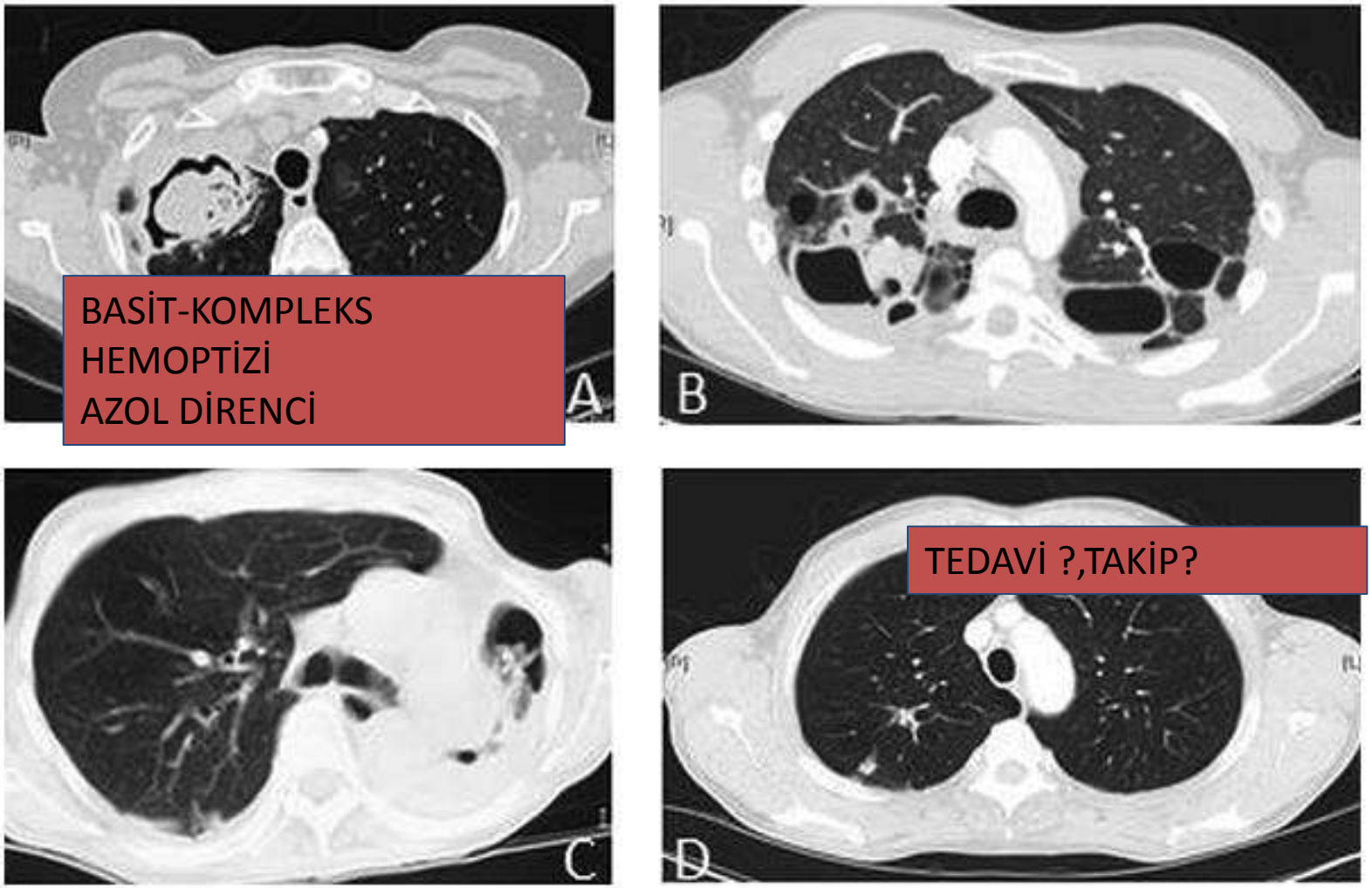
Chronic pulmonary aspergillosis

Infection of the lung by *Aspergillus*



KLİNİK

KPA



BASİT-KOMPLEKS
HEMOPTİZİ
AZOL DİRENCİ

TEDAVİ ?,TAKİP?

Figure 3 CT scans from patients with various forms of chronic pulmonary aspergillosis. (A) Simple aspergilloma; (B) Chronic cavitary pulmonary aspergillosis; (C) Chronic fibrosing pulmonary aspergillosis; (D) Aspergillus nodule.

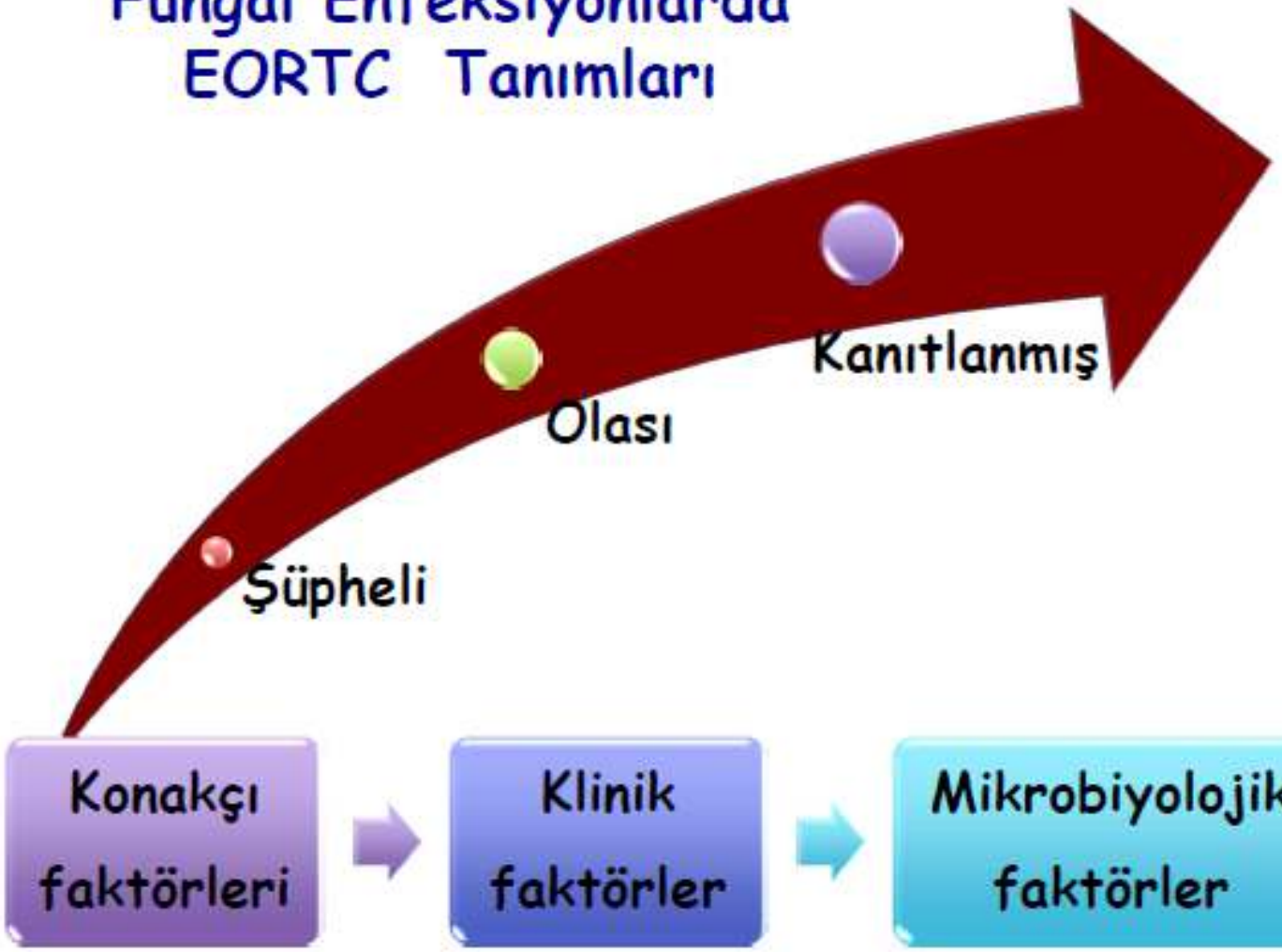
Aspergillus spesifik IgG, KÜLTÜR, PCR

Aspergilloz tanısı

- Klinik ve radyolojik bulgular
- Direk mikroskobik incelemede mantar elemanları
- Kültürde *Aspergillus* üremesi
- Galaktomannan antijen pozitifliği
- Histopatolojik olarak hiflerin görülmesi
- Konak faktörleri
- Nötropeni, ateş, uzamış antibiyotik kullanımı, immünsüpresyon öyküsü invaziv mantar enfeksiyonu öyküsü, AIDS öyküs

Richardson MD, Hope W. *Aspergillus*, In: Clinical Mycology Pfaller MA Eds.). Churchill Livingstone Elsevier, 2009: 271-296.

Fungal Enfeksiyonlarda EORTC Tanımları

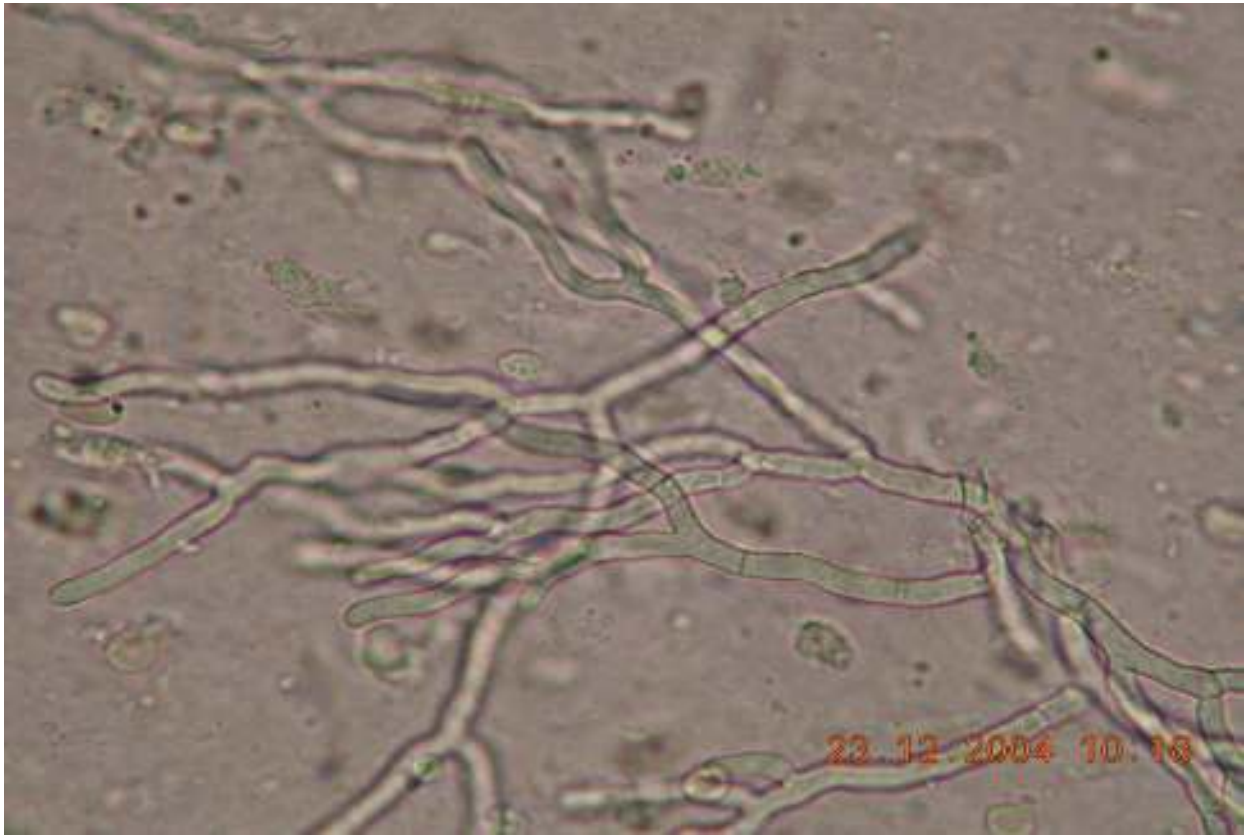


TANI

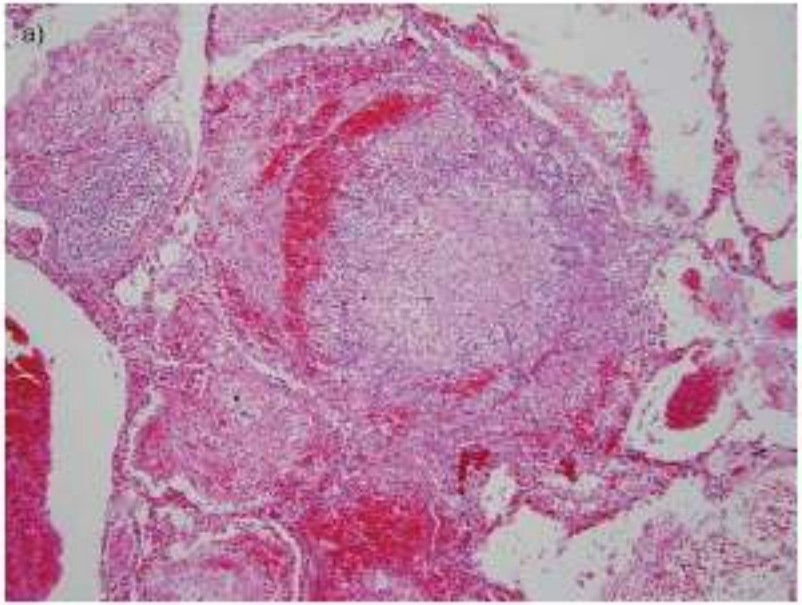
- Histopatoloji
- Kültür
- Biyolojik belirteçler
- PCR
- Diğer metodlar

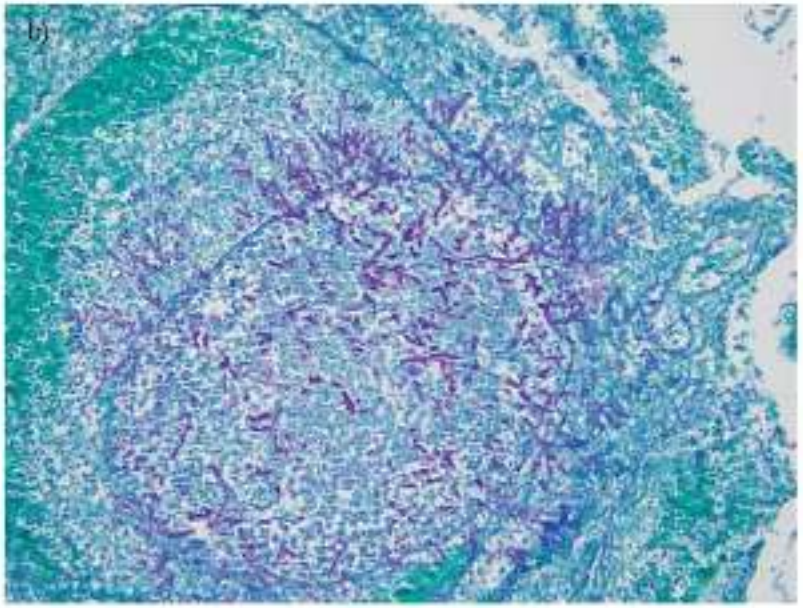
Solunum yolu örnekleme > Kan örnekleme !!!

DİREKT İNCELEME RESMİ



Histopatolojik değerlendirme

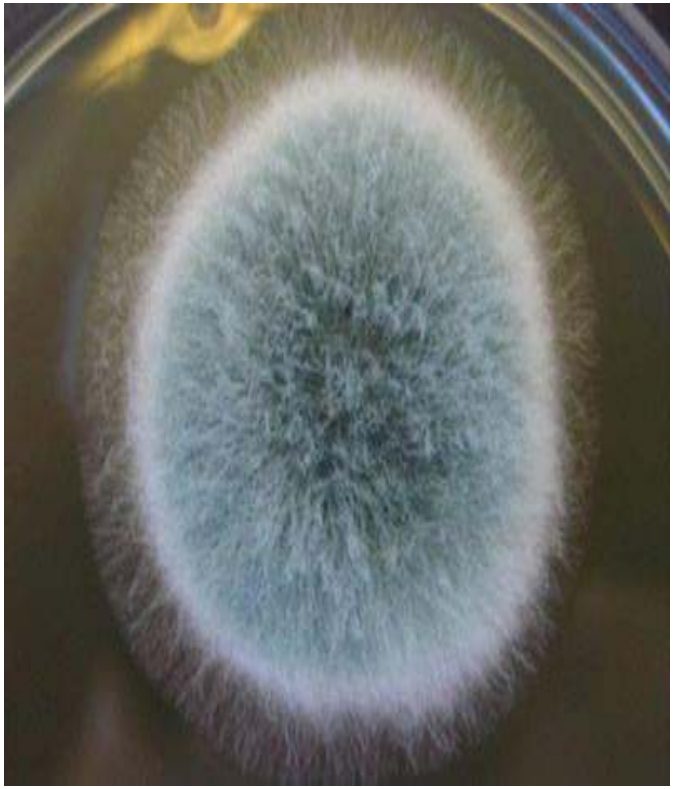




HE

Methenamin

Balgam kültürü



- İmmunnormal hastada balgamda aspergillus üremesi

  Kolonisazyon %92,

  IPA %4,5

  Eur J Clin Microbiol Infect Dis 2004; 23: 491–494

- İmmundüşkün hastada balgamda aspergillus üremesi

  Duyarlılık %80-90

J Infect Dis1985; 152: 572–576

Bronkoalveolar lavaj

- %50 duy; %97 özgüllük
- Kültür-direnç profili (A. Terreus?)
- Antijen testi

Ann Hematol2003; 82: Suppl. 2, S118–S126

Bone Marrow Transplant1999; 24: 1195–1199

Cancer2004; 101:1594–1600

GALAKTOMANNAN

- Bazı mantarların hücre duvarında bulunur
- Akut enfeksiyon sırasında kan dolaşımına saçılır
- Cut-off 0.5
- Haftada 2 kez
- Tedaviden etkilenir
- Yanlış pozitiflik: Piperasilin-tazobaktam
- Duyarlılık %71
- Özgüllük %89

Anaissie EJ et al. Best Practice Research Clinical Hematology 2008
Pogano L et al. Blood Reviews 2010

GALAKTOMANNAN

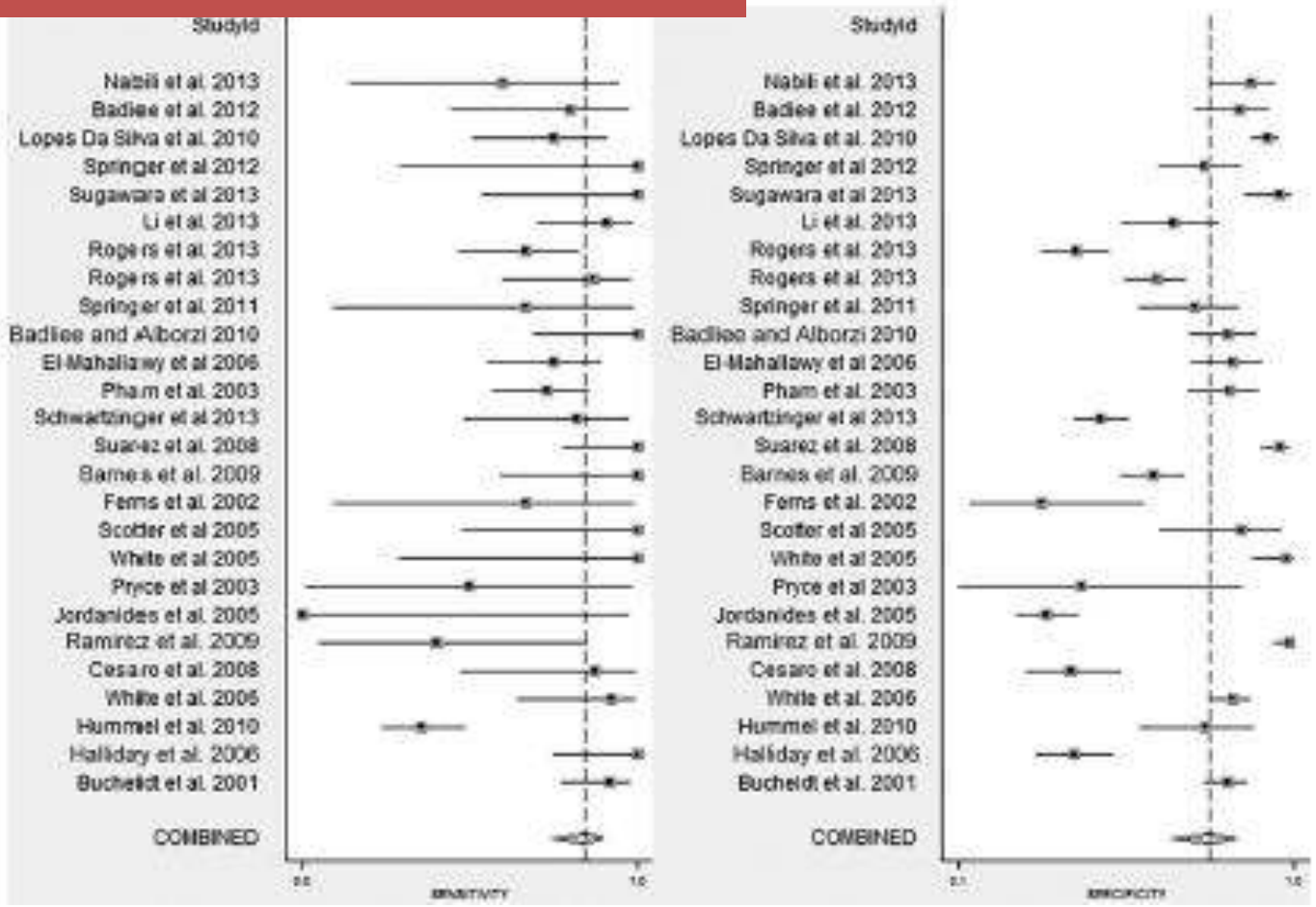
- İPA tanısı
- Tedaviye yanıt – prognoz
- İmmün rekonstitüsyon ayırıcı tanısı

  Anaissie EJ et al. Best Practice Research Clinical Hematology 2008
- BAL'da Galaktomannan bakılması yararlı

  Sherif R et al. Curr Opin Pulm Med 2010

PCR

DUYARLILIK % 84
ÖZGÜLLÜK %76



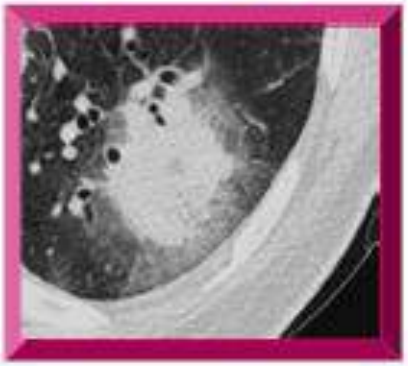
PCR in Diagnosis of Invasive Aspergillosis: a Meta-Analysis of Diagnostic Performance

Erkenden BT
Seri BT

İnvazif Aspergilloz'da BT Bulguları

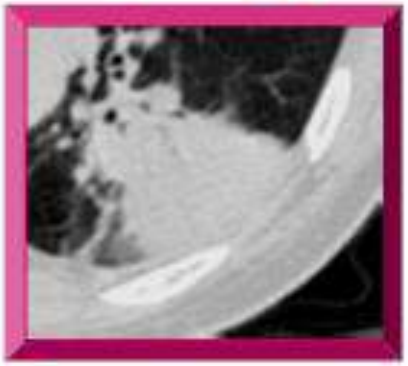
Halo belirtisi

0 - 5 g



Konsolidasyon

5 - 10 g



Hava-hilal belirtisi

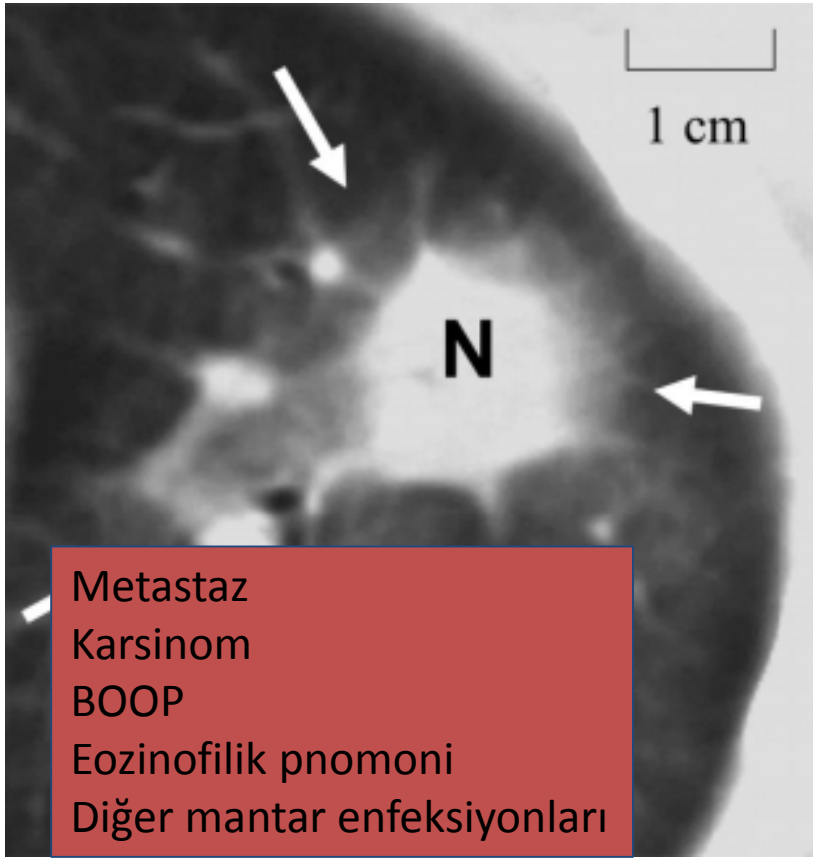
10 - 20 g

kavite

Nötropeni

Caillot et al. 2001

Tomografi



Metastaz
Karsinom
BOOP
Eozinofilik pnomoni
Diğer mantar enfeksiyonları

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

RADYOLOJİ

Bilgisayarlı Tomografi (BT)

- Düz grafiden daha duyarlı
- FEN'de antibakteriyel tedaviye rağmen ateş devam ediyor ve açıklanamamıyorsa
- En erken radyolojik belirti nodül
- Halo belirtisi(erken dönemde): Etrafı alveolar hemorajiyi temsil eden buzlu-cam opasitesi ile çevrilmiş makronodül
- Hava-hilal belirtisi

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

Radyolojik çalışma bulguları

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

NOTE. Patients may have >1 type of lesion.

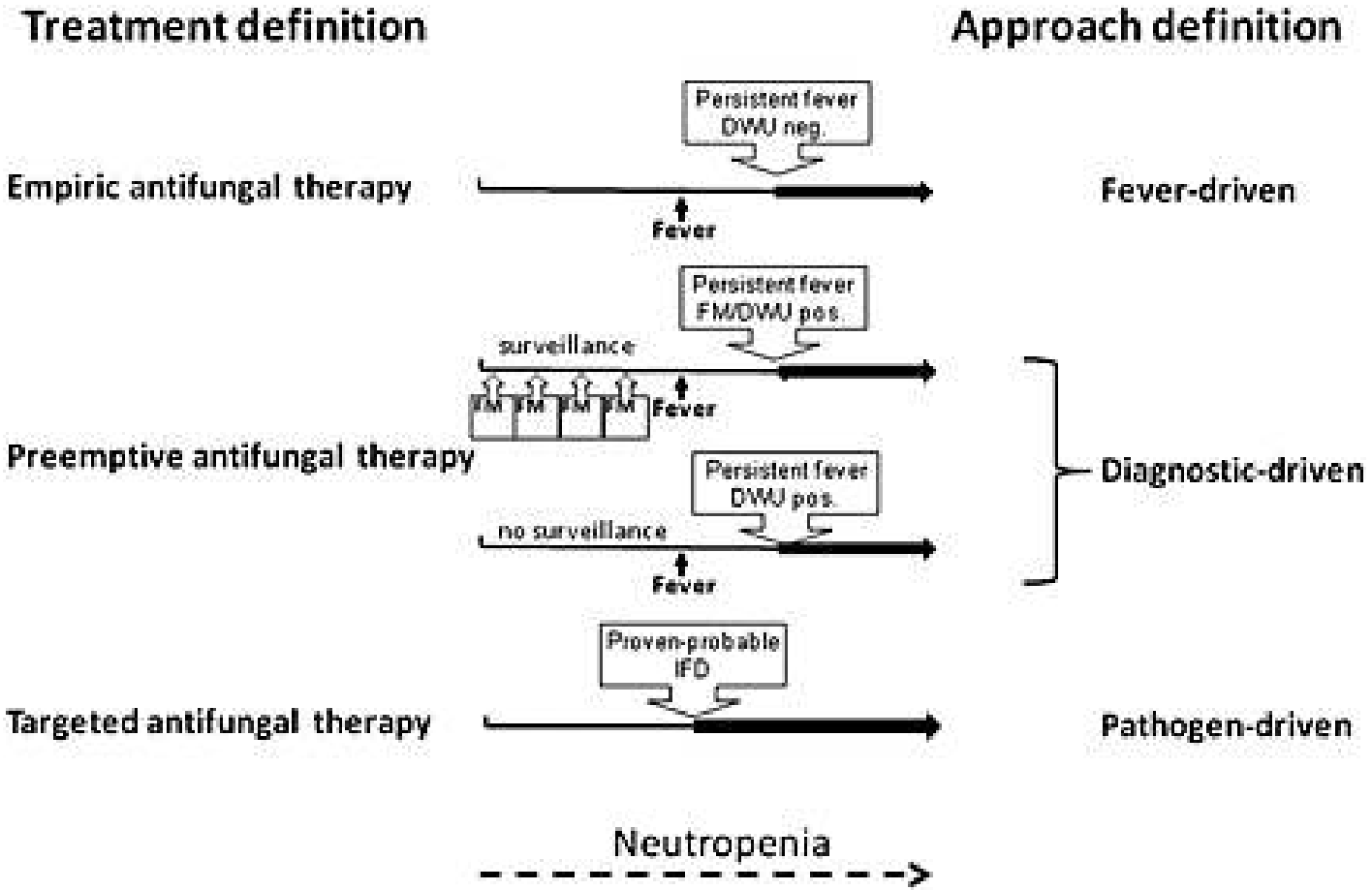
[a] Includes macronodules with or without halo sign and infarct-shaped macronodules.

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

[c] Includes infarct-shaped consolidations.

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

ANTİFUNGAL TEDAVİ



FM: fungal marker; IFD: invasive fungal disease; DWU: diagnostic work-up (FM + CT + other exams)

Antifungal therapy

ANTİFUNGAL TEDAVİ

(PRİMER PROFLAKSİ)

ECIL 5 Recommendations

	Acute myeloid leukaemia patients undergoing intensive chemotherapy		
	Antifungal drug	*Grading*	*Comments*
EFISG -	Fluconazole (400 mg q24)	BI	Only recommended if the incidence of mould infections is low. Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach.
EFISG DII	Itraconazole oral solution (2.5 mg/kg q12h.)	BI	Recommended if baseline incidence of mould infections is high. May be limited by drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations.
EFISG AI	Posaconazole (oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1)	AI	Recommended if baseline incidence of mould infections is high. Given the increased absorption of the tablet, it is likely that need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis or GvHD).
EFISG -	Voriconazole (200 mg q12h)	BII	Recommended if baseline incidence of mould infections is high. It is recommended to monitor serum drug concentrations.

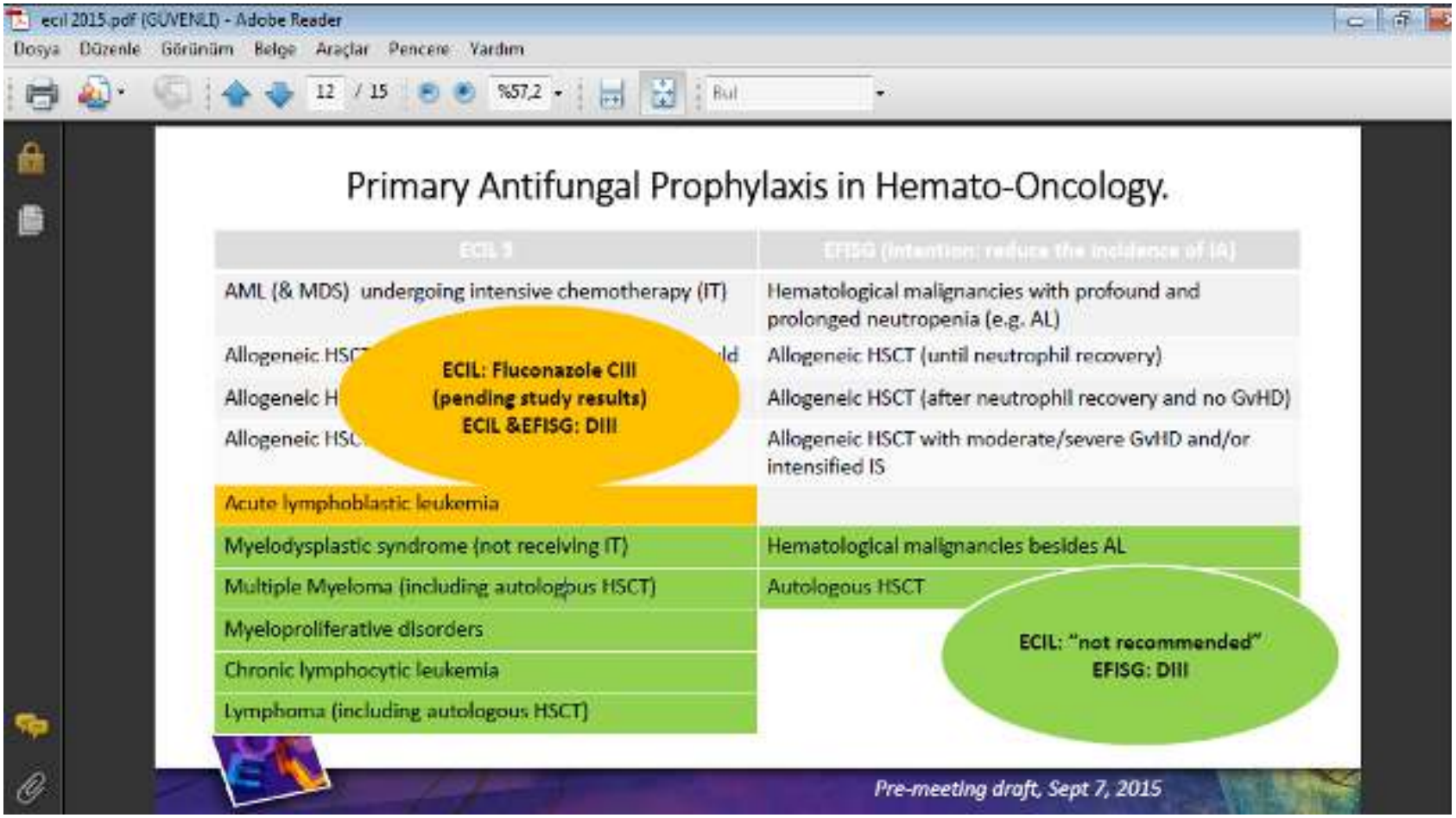
Azoles should not be used empirically in case of prior mould-active azole prophylaxis.

ECIL 5 Recommendations

Acute leukaemia patients undergoing induction chemotherapy

Antifungal drug	*Grading*	*Comments*	
Echinocandins IV	**CII**	Insufficient data on efficacy and tolerability	**EFISG CII_t**
Amphotericin B liposomal IV	**CII**	Insufficient data on dose, frequency and duration as well as on efficacy and tolerability	**EFISG CII**
Amphotericin B lipid associated IV	**CII**	Insufficient data on dose, frequency and duration as well as on efficacy and tolerability	**EFISG CII_h**
Aerosolized liposomal amphotericin B	**BI**	Only when combined with oral fluconazole	**EFISG BI**
Amphotericin B desoxycholate IV	**AII-against**		**EFISG -**
Aerosolized amphotericin B deoxycholate	**AI-against**		

Pre-meeting draft, Sept 7, 2015



Primary Antifungal Prophylaxis in Hemato-Oncology.

ECIL 3	EFISG (intention: reduce the incidence of IA)
AML (& MDS) undergoing intensive chemotherapy (IT)	Hematological malignancies with profound and prolonged neutropenia (e.g. AL)
Allogeneic HSC[illegible]ld	Allogeneic HSCT (until neutrophil recovery)
Allogeneic H	Allogeneic HSCT (after neutrophil recovery and no GvHD)
Allogeneic HSC	Allogeneic HSCT with moderate/severe GvHD and/or intensified IS
Acute lymphoblastic leukemia	
Myelodysplastic syndrome (not receiving IT)	Hematological malignancies besides AL
Multiple Myeloma (including autologous HSCT)	Autologous HSCT
Myeloproliferative disorders	
Chronic lymphocytic leukemia	
Lymphoma (including autologous HSCT)	

ECIL: Fluconazole CIII (pending study results) ECIL &EFISG: DIII

ECIL: "not recommended" EFISG: DIII

Pre-meeting draft, Sept 7, 2015

Primary Antifungal Prophylaxis in Hemato-Oncology.

ECIL 5	EFISG (intention: reduce the incidence of IA)
AML (& MDS) undergoing intensive chemotherapy (IT)	Hematological malignancies with profound and prolonged neutropenia (e.g. AL)
Allogeneic HSCT - pre-engraftment @ low risk for mould	Allogeneic HSCT (until neutrophil recovery)
Allogeneic HSCT - pre-engraftment @ high risk	Allogeneic HSCT (after neutrophil recovery + no GvHD)
Allogeneic HSCT - GvHD	Allogeneic HSCT with moderate/severe GvHD and/or intensified IS
Acute lymphoblastic leukemia	
Myelodysplastic syndrome (not receiving IT)	Hematological malignancies besides AL
Multiple Myeloma (including autologous HSCT)	Autologous HSCT
Myeloproliferative disorders	
Chronic lymphocytic leukemia	
Lymphoma (including autologous HSCT)	

EFISG D III

ECIL 5 Recommendations for allogeneic HSCT recipients

Antifungal prophylaxis*	Pre-engraftment Low risk for moulds	Pre-engraftment High risk for moulds	GvHD
Fluconazole	A-I	A-III - against	A-III against
Itraconazole	B-I	B-I	B-I
Voriconazole	B-I	B-I	B-I
Posaconazole OS/Tablet	B-II	B-II	A-I
Micafungin	B-I	C-I	C-II
Caspofungin /anidulafungin	No data	No data	No data
Liposomal Amphotericin B	C-II	C-II	C-II
Aerosolized amphotericin B plus fluconazole	C-III	B-II	No data

D-I
C-I
$B\text{-}II_t$
CI
$B\text{-}II_t$
C-II
C-II
C-III

ANTİFUNGAL TEDAVİ

(AMPİRİK TEDAVİ) TARTIŞALIM !!

ANTİFUNGAL TEDAVİ

(PREEMPTİF TEDAVİ) TARTIŞALIM !!

DAHA AZ ANTİFUNGAL ?

- GM ve Toraks BT'ye dayanarak preemptif tedavi yaklaşımı
- Antifungal kullanımında azalma %35-%7.7(%78)
- Mukormikoz ?

Maertens J et al. Clin Infect Dis 2005

Empirik vs Preemptif Tedavi (PREVERT)

Mortalite fark yok

- **Preemptif Tedavi**
  - Nefrotoksisite oranı azalmadı
  - Antifungal kullanımı % 35 oranında azaldı

    (% 39.2 vs 61.3%; P=0.001)
  - Ateş başladıktan sonra tedaviye kadar geçen süre arttı

    (13 vs 7 gün, P=0.01)
- **Ampirik Tedavi**
  - İndüksiyon tedavisi alan AML - daha iyi sağkalım

Cordonnier C, et al. CID 2009, 48: 1042-51

ALT GRUP ANALİZİ ?

- İnvazif fungal enfeksiyonlar preemptif kolda anlamlı olarak yüksek(4-13, $p<0.02$)
- İnvazif fungal enfeksiyonların önemli bir kısmı indüksiyon tedavisi alan grupta

Cordonnier C et al. Clin Infect Dis 2009

ANTİFUNGAL TEDAVİ
HEDEFE YÖNELİK TEDAVİ

TEDAVİ

Organ yetmezliği
(böbrek,KC,nörotoksisite)
toksisite
tolerabilite

- **BAŞLANGIÇ TEDAVİ?**
- VOR+ECHINO ∞ VOR ???
- Lipid amphotericin B veya isavuconazole
- Azol deneyimi olan hastada ampirik tedavi ???
- Mukor???
- İlaç etkileşimi
- Antifungal direnç (A. Terreus,A. Calidoustus, A. lentulus)

- **KURTARMA TEDAVİSİ** ??

Çok seçenek yok

TEDAVİ

- Vorikonazol serum düzeyi takibi >2, <5.5 mcg/ml
- Görme değişiklikleri
- Hallusinasyon
- QTc uzaması (diğer azol kısaltıyor!!)
- Nöropati
- SSS etkileri
- Alopesi,ağız yaraları
- Uzun dönemede;Deri kanseri riski

TEDAVİ

- Posakonazol ; süspansiyon-tablet ?
- Isavukonazol-
- Itrakonazol
- Amfoterisin B – daha çok doz daha iyi ???
- Ekinokandinler
- Kombinasyon tedavileri (çelişkili sonuçlar)

TEDAVİ

Aspergilloz - Vorikonazol

- Vorikonazol ile AmB-d
- 12. haftada sağkalım

- VRC %71 -AmB-d %58

Herbrecht R et al. N Engl J Med 2002

TEDAVİ

Aspergilloz – Lipozomal-AmB

AmbiLoad çalışması

- 3 mg/kg ile 10 mg/kg
- 12. haftada sağkalım -3 mg/kg %72 -10 mg/kg %59

Cornely OA et al. Clin Infect Dis 2007

TEDAVİ

Aspergilloz - Kaspofungin

- 61 İnvazif Aspergilloz(yüksek olasılıklı veya kanıtlanmış)
- %85 nötropenik
- 12. haftada sağkalım %53

Viscoli C et al. J Antimicrob Chemother 2009

- 24 Allojeneik HKHT
- İnvazif Aspergilloz(yüksek olasılıklı veya kanıtlanmış)
- 12. haftada sağkalım %50

Herbrecht R et al. Bone Marrow Transplant 2010

TEDAVİ

- İmmunmodulasyon
- GCSF

TEDAVİ

CERRAHİ

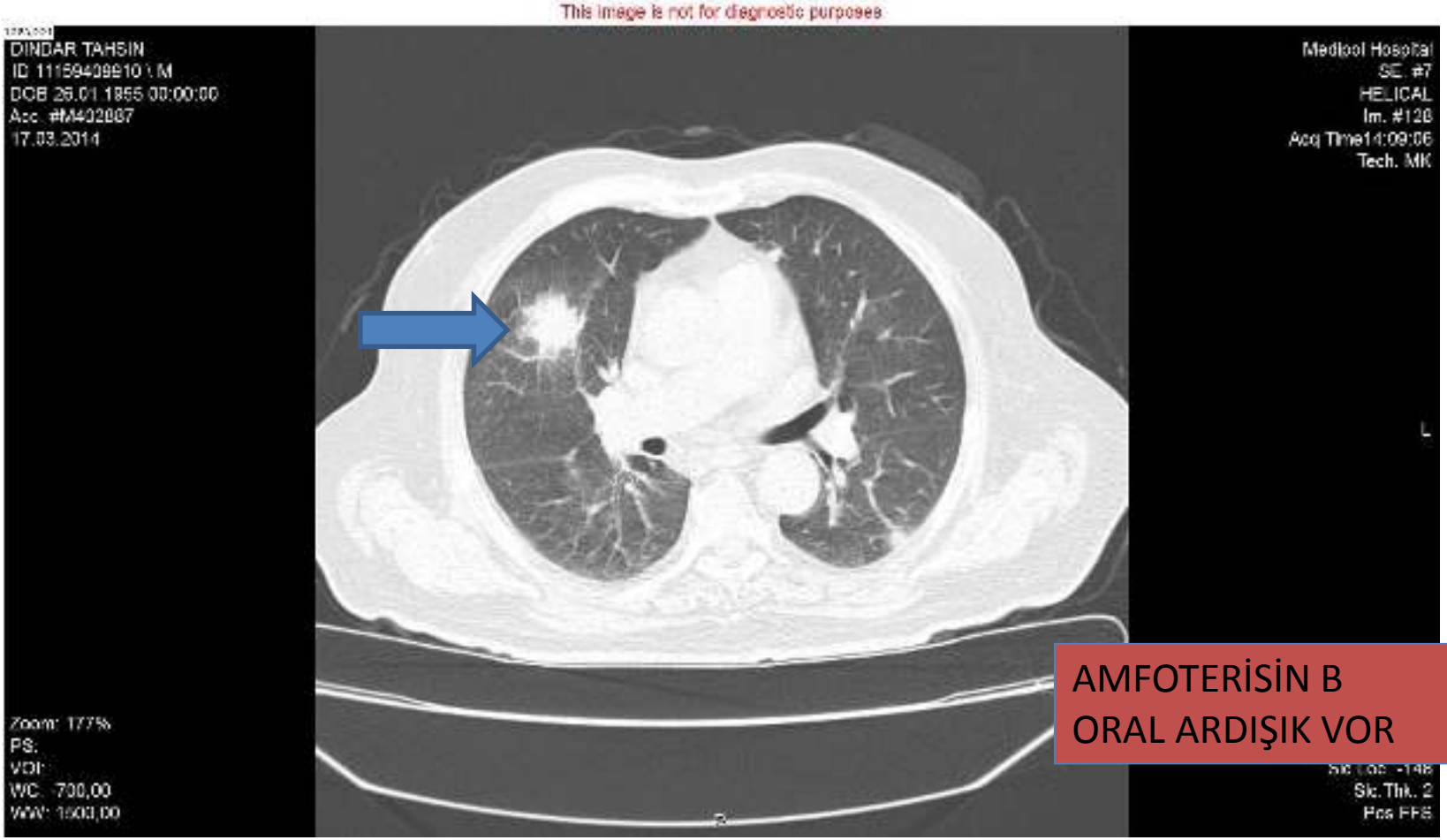
a. Aspergillus rinosinuzit
b. Tek AC lezyonu (kavite içi)- kanama?
c. Endokardit
d. Perikardit
e. Ampiyem
f. Osteomyelit
g. Protez enfeksiyonları

IPA HASTALARINDAN ÖRNEKLER

60 Y, ERKEK HASTA

- Sol yan ağrısı, öksürük
- Dahiliye, göğüs hastalıkları, göğüs cerrahisi vs.
- Derinleşen trombositopeni-ITP; Uzun süre yüksek doz steroid kullanımı
- Trombopeniye eklenen pansitopeni; Kemik iliği biyopsisi
- Tanı: Prekürsör B hücreli ALL
- GMALL 2003
- IDA-FLAG

İLK KT SONRASI

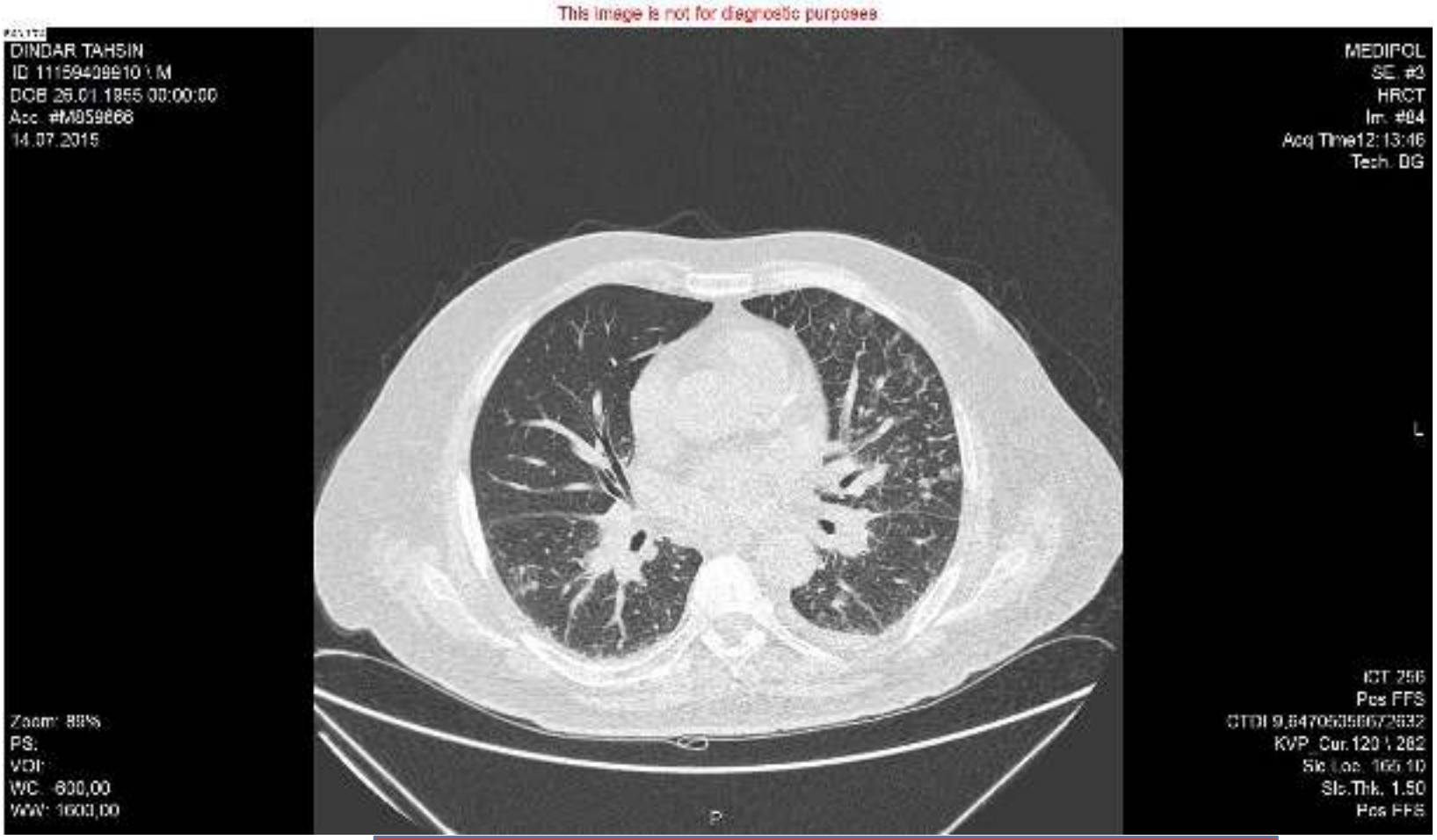


AMFOTERİSİN B
ORAL ARDIŞIK VOR

AYAKTA PARANOŞİ-SİYAH RENK
GALAKTOMANNAN: 0.15

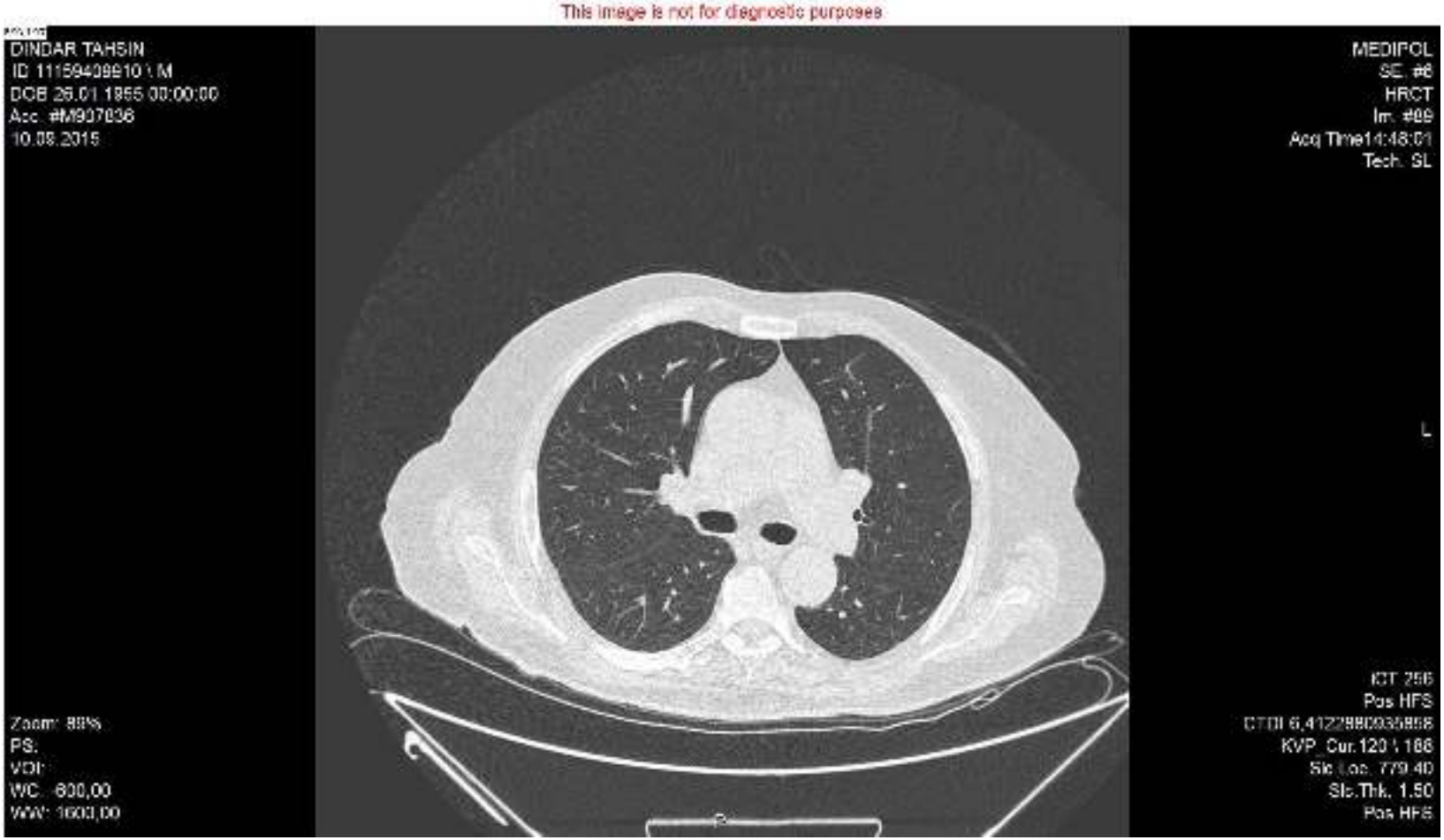
TAKİP

VE NAKİL SONRASI



POSAKONAZOL PROFLAKSİSİ ALTINDA
GALAKTOMANNAN 1.6

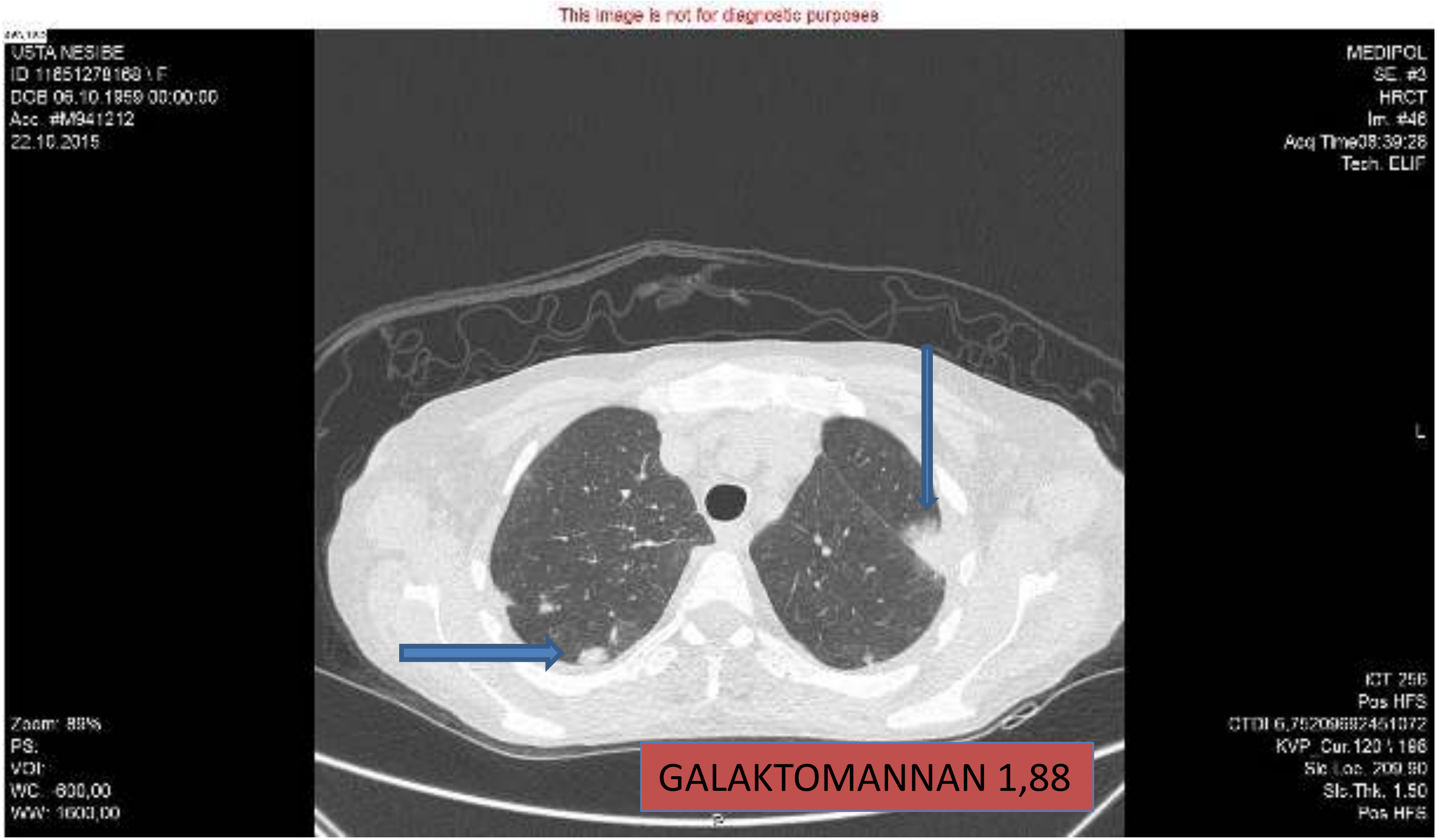
VE MUTLU SON



GALAKTOMANAN 0.36

56 YAŞ, KADIN HASTA

- 11 AY ÖNCE KADAVRADAN BÖBREK NAKLİ
- HALSİZLİK VE NEFES DARLIĞI-YATIRILDI
- WBC:9000, CRP: 52
- TAKROLİMUS, STEROİD, MYCO ALIYOR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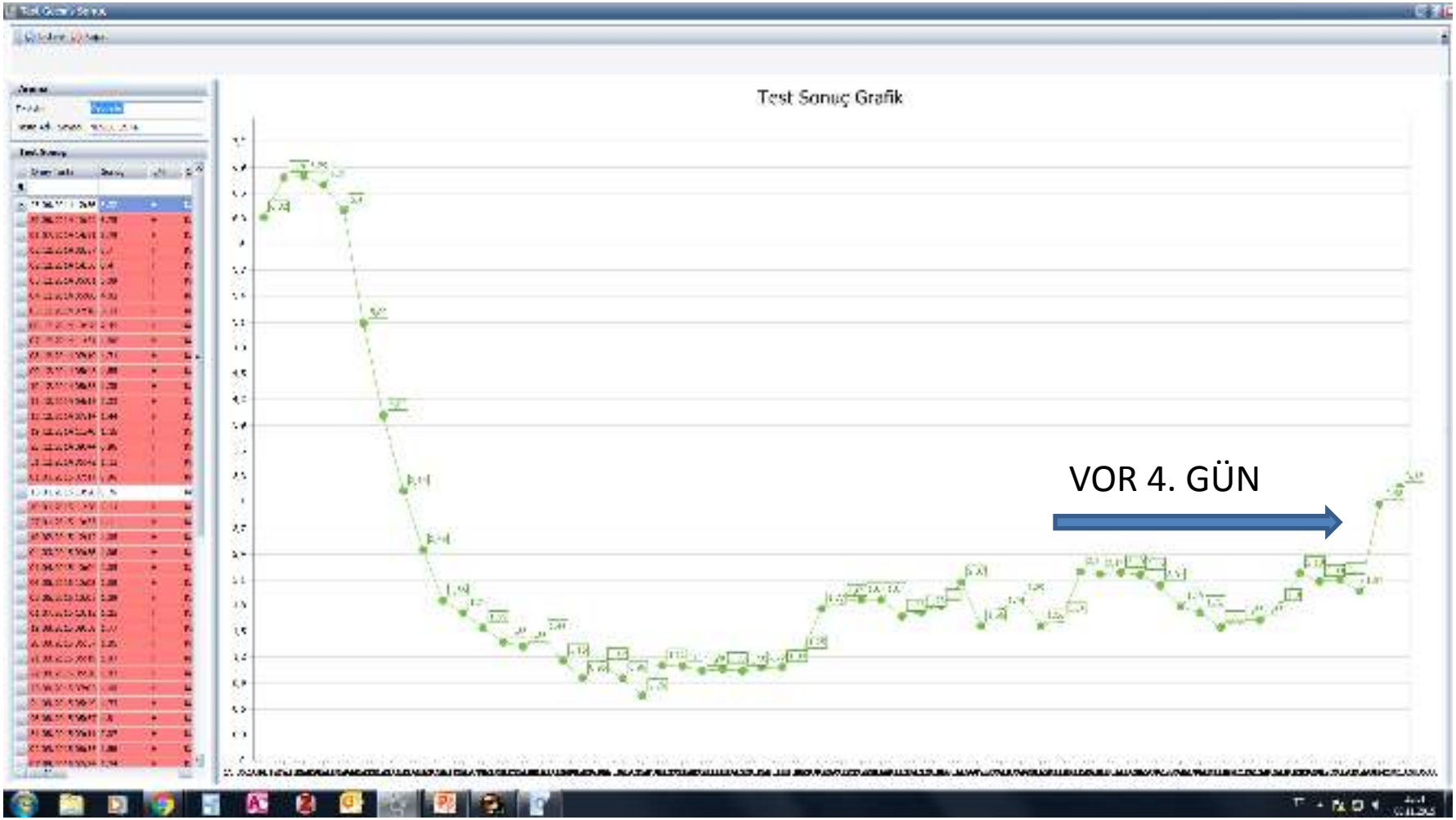
GALAKTOMANNAN 1,88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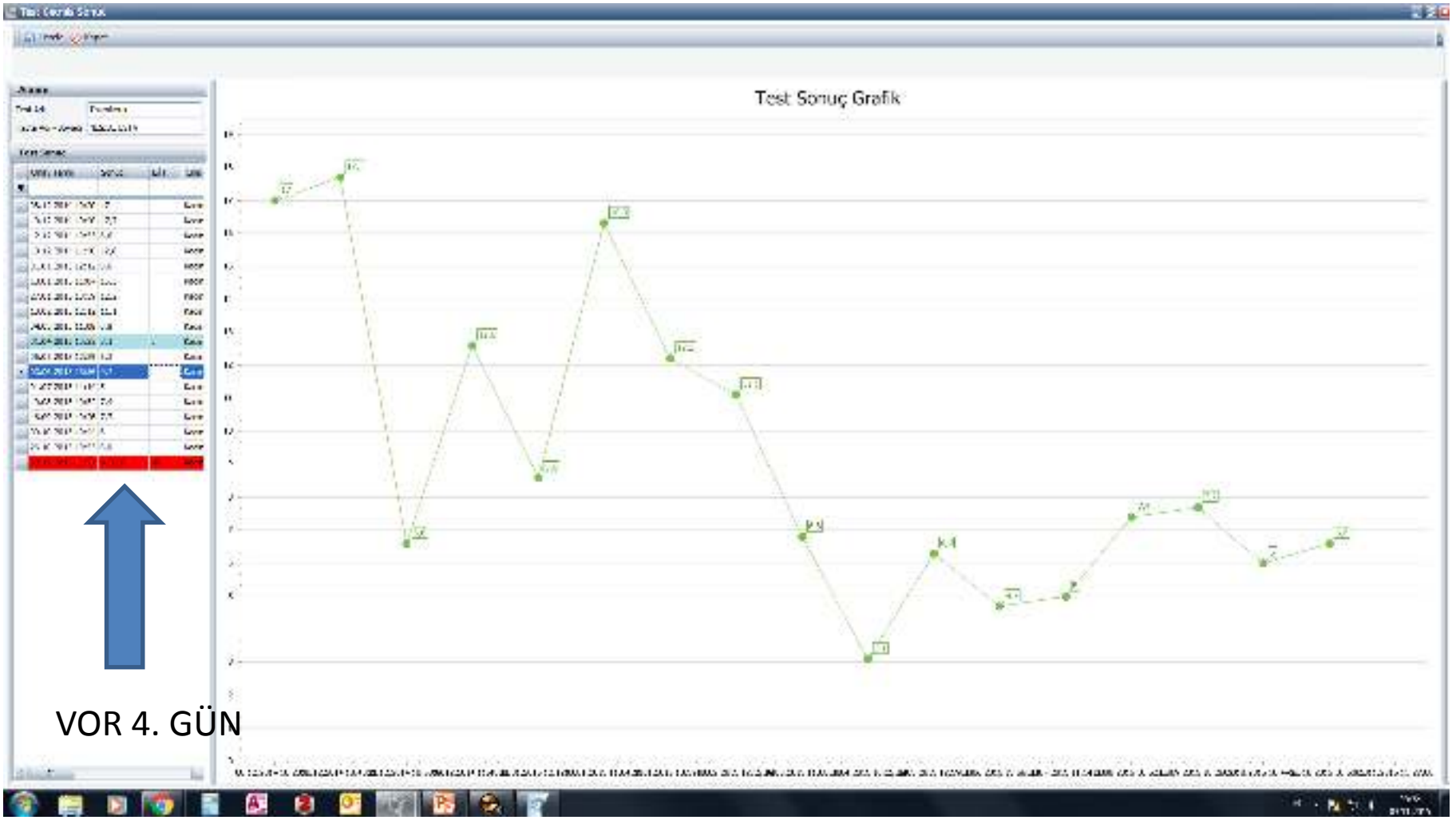
VOR 4. GÜN



ŞİDDETLİ BULANTI KUSMA, İNTOLERANS