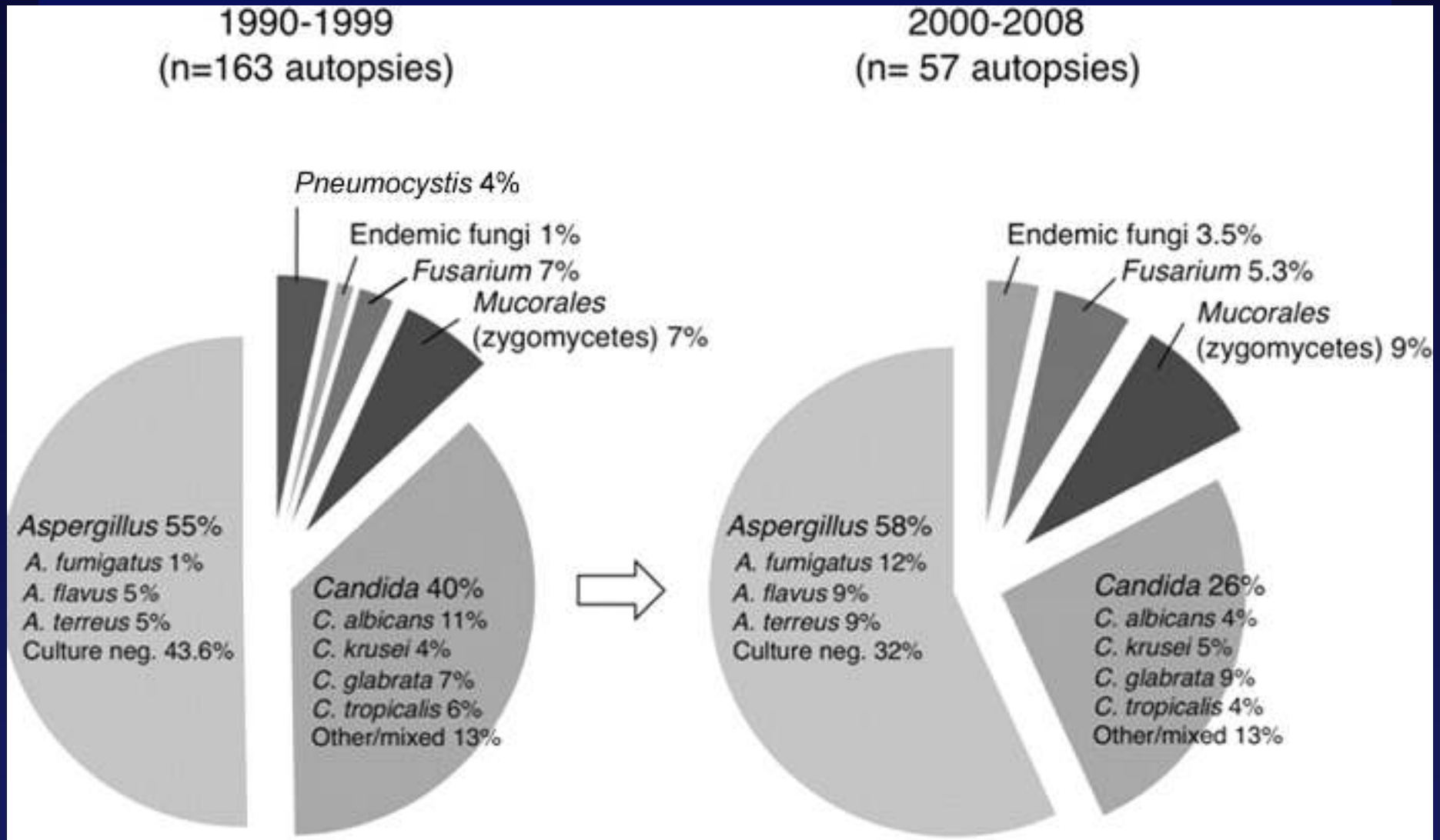
İNVAZİF KÜF ENFEKSİYONLARINDA TEDAVİ

Prof Dr Zekaver Odabaşı

Marmara Üniversitesi Tıp Fakültesi

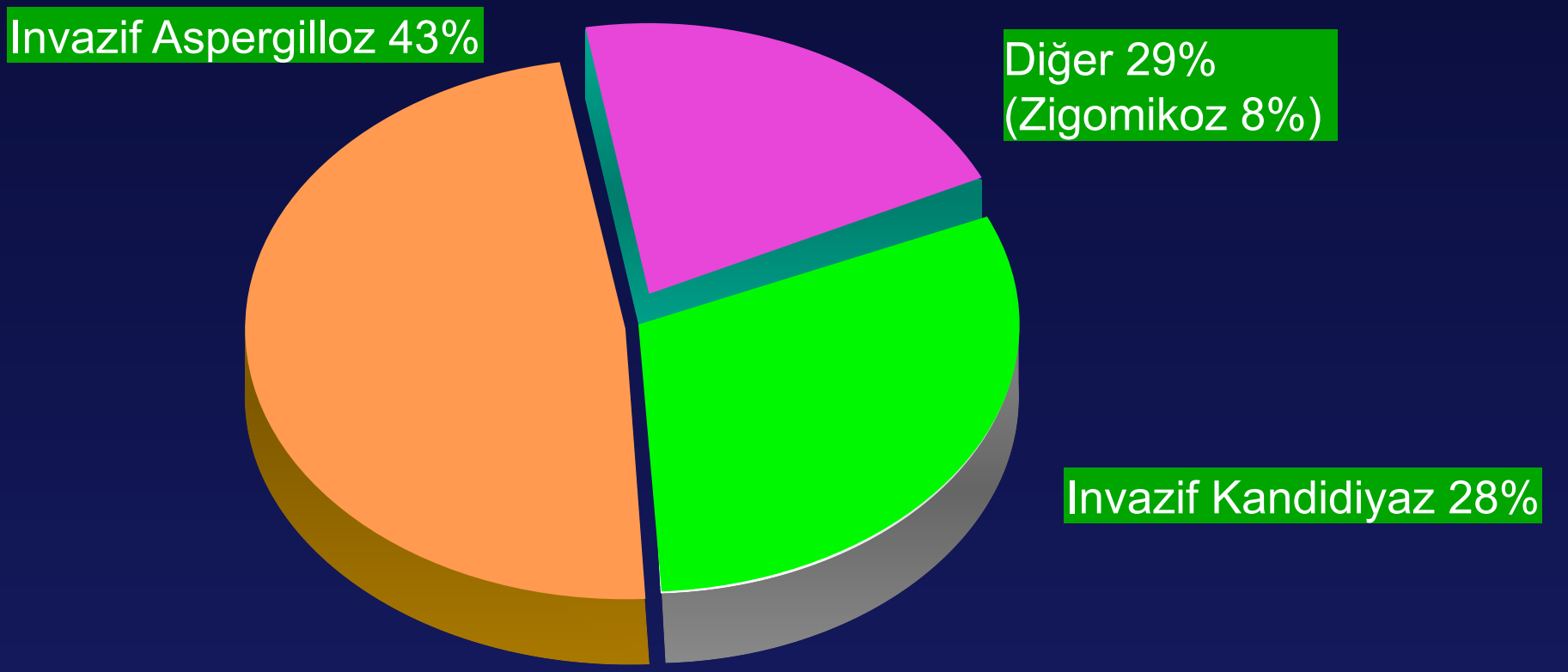
Lösemi Hastalarında Görülen İnvazif Fungal Enfeksiyonların Dağılımı



Leventakos et al. Clin Infect Dis. 2010;50:405-415

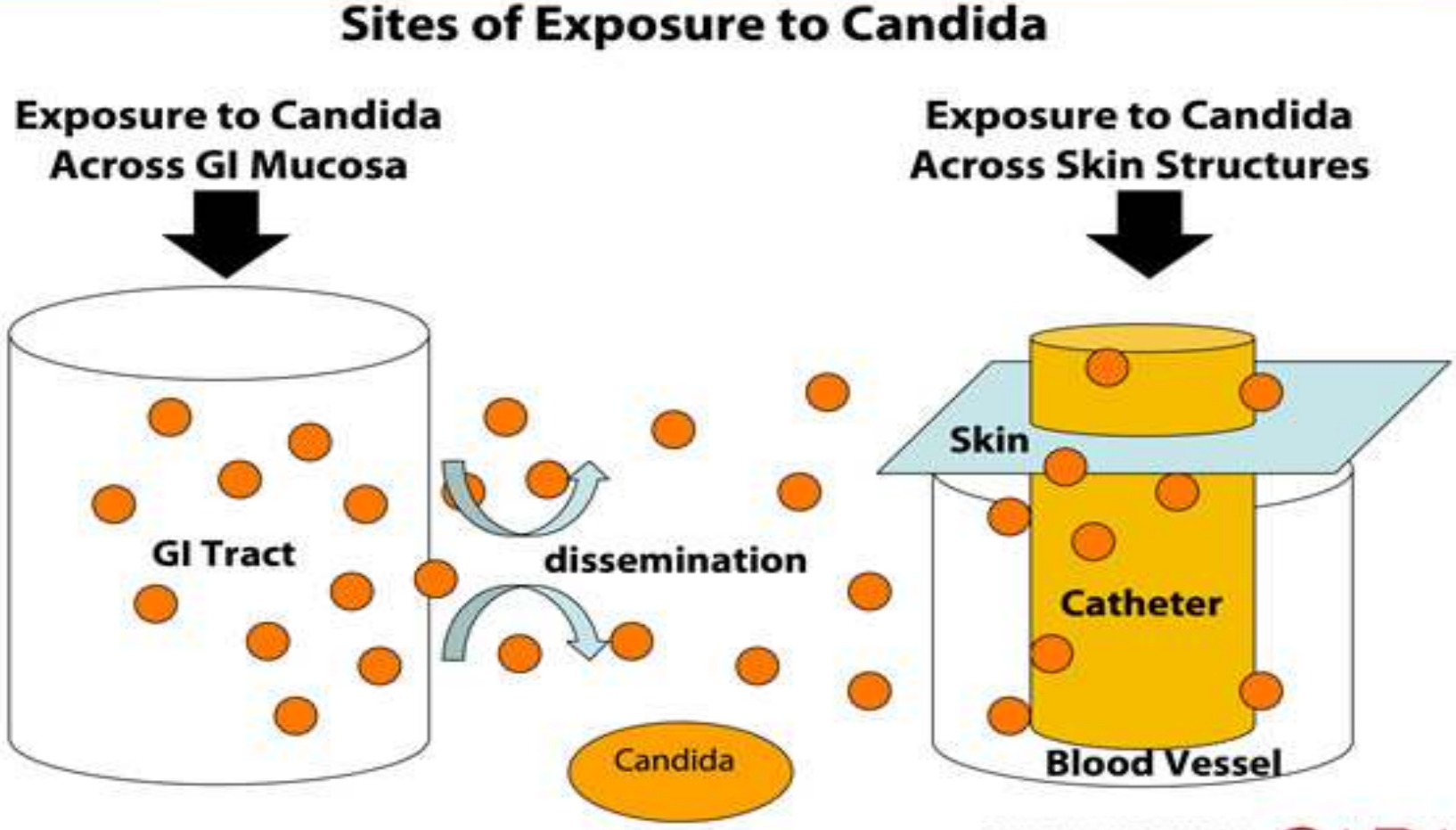
* note: some patients had multiple pathogens, therefore total % exceeds 100

TRANSNET – KIT Hastalarında IFI (2001-2006)

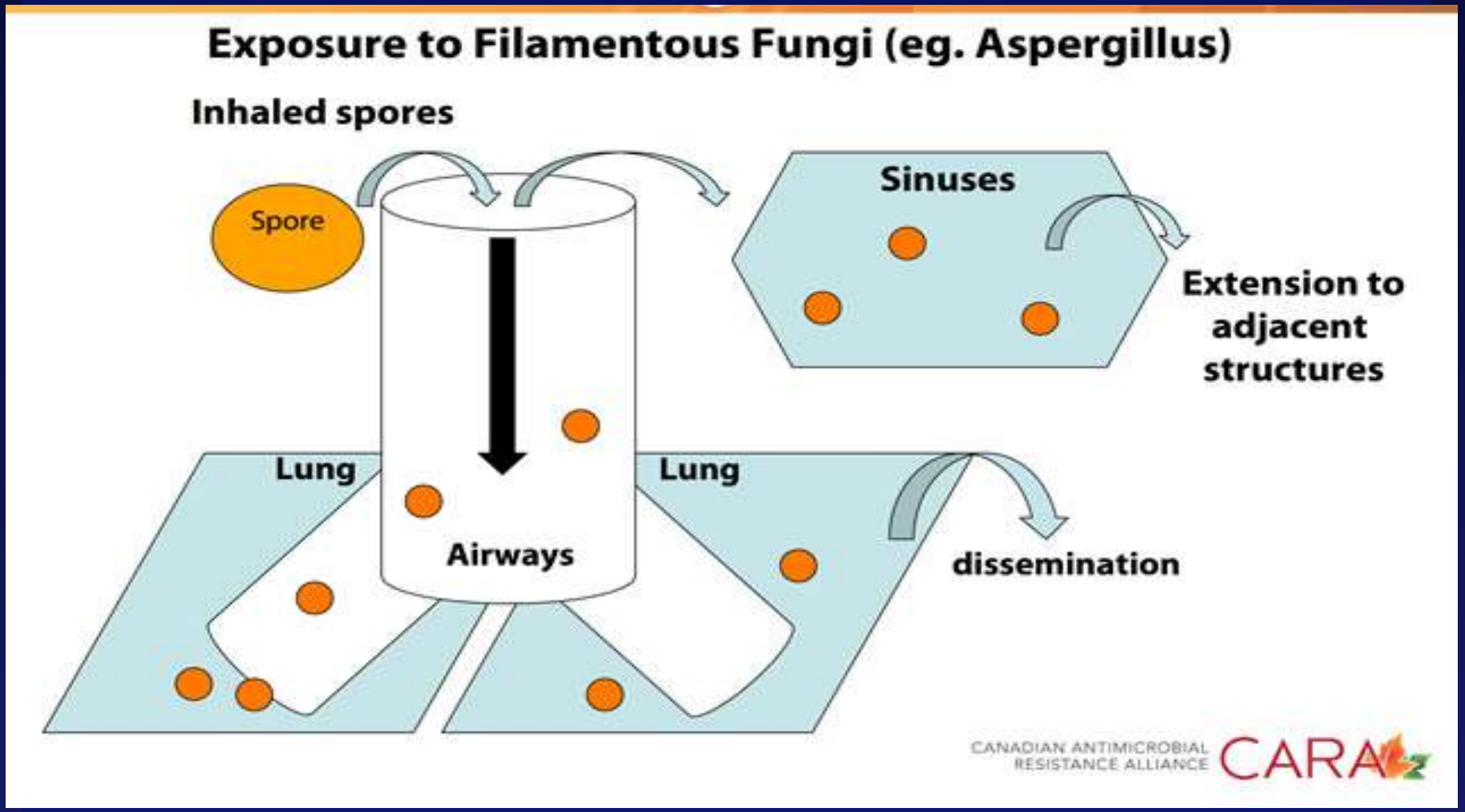


Kontoyiannis D, CID, 2010

Kandida Enfeksiyonları Genelde Endojen Kökenlidir



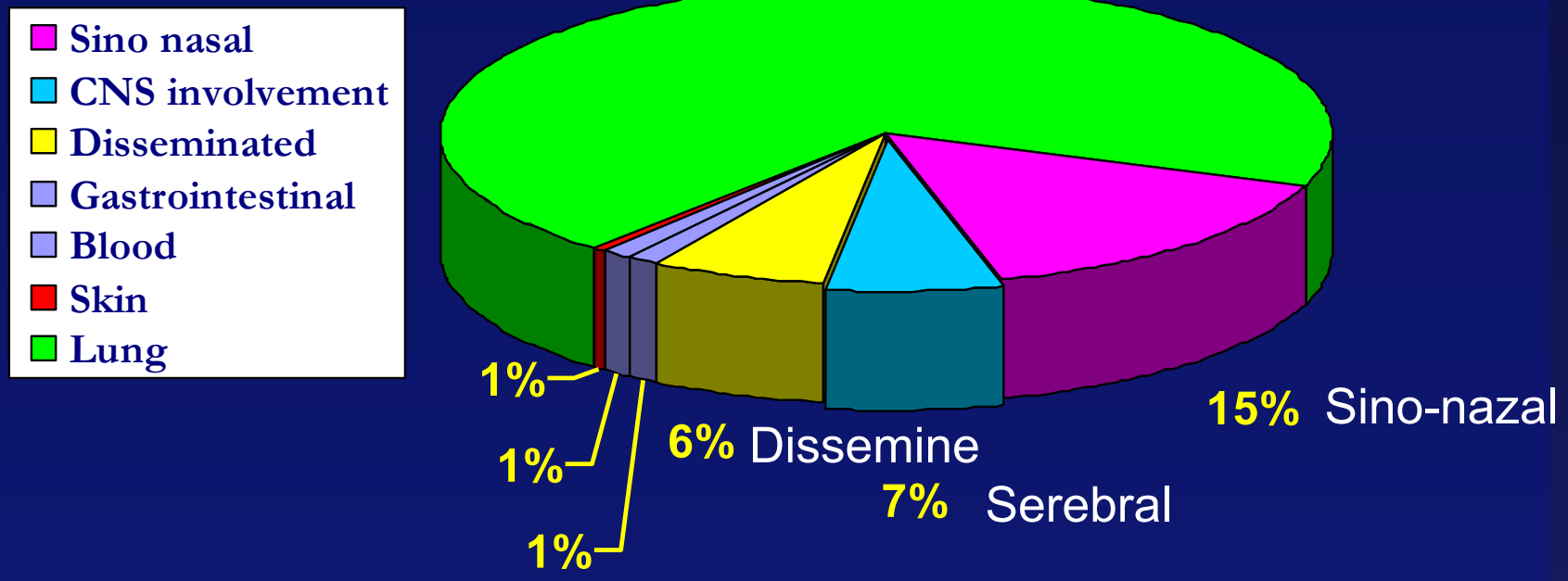
Küf Enfeksiyonları İse Genelde Eksojen Kökenlidir Sporların İnhalasyonu ile Olur



İnvazif Aspergilloz Risk Faktörleri

Kronik granülomatöz hastalık Allogeneik ilik nakli ve GVHH gelişmesi Akciğer nakli AML indüksiyon kemoterapisi veya refrakter Yüksek doz steroid veya >3 hafta steroid tedavisi	**Yüksek risk**
GVHH olmayan Allogeneik ilik nakli ALL AML (konsolidasyon) MDS KLL Kalp, akciğer, ince barsak nakli	**Orta risk**
Multiple myeloma KOAH alevlenme AIDS Non-Hodgkin lenfoma Otolog ilik nakli Solid tümörler Otoimmün hastalıklar	**Düşük risk**

Tutulum Yerleri



Pagano et al, Haematologica 2001

Pulmoner İFİ etkenleri

Fungal etken	Sayı
Aspergillus spp	**80**
Aspergillus fumigatus	12
Aspergillus flavus	9
Aspergillus niger	2
Aspergillus terreus	1
Cryptococcus spp	**30**
Cryptococcus neoformans	30
Candida spp	**20**
Candida albicans	9
Candida tropicalis	4
Candida glabrata	4
Candida parapsilosis	2
Diğerleri	**10**
Mycelium sterila	**3**
Penicillium marneffei	**2**
Coccidioides immitis	**1**
Mucor spp	**1**
Rhizopus spp	**1**
Histoplasma capsulatum	**1**
Rhodotorula glutinis	**1**

Chen KY, Chest. 2001

Küf etkili antifungal ajanla profilaksi yapılan allogeneik ilik nakli hastasında galaktomannan antijen takibi yapalım mı?

A. Duyarlılığı çok azaltacağından gerek yok
B. Fungal enfeksiyon şüphesi olursa bakılmalı
C. Mutlaka haftada düzenli iki kez bakılmalı

Antifungal Therapy Decreases Sensitivity of the *Aspergillus* Galactomannan Enzyme Immunoassay

Kieren A. Marr,[1,2] Michel Laverdiere,[3] Anja Gugel,[1] and Wendy Leisenring[1,2]

[1]Fred Hutchinson Cancer Research Center and [2]University of Washington, Seattle, Washington; and [3]Hopital Maisonneuve-Rosemont, Montreal, Canada

Background. Reported sensitivity of the galactomannan enzyme immunoassay as an early diagnostic test for invasive aspergillosis (IA) has been widely variable, ranging from 29% to 100% in earlier clinical studies.

Methods. Studies performed to date have analyzed performance using per-patient calculations, limiting their ability to measure the impact of clinical variables that change over time, such as receipt of preventive antifungal therapy. In our study, performance of the test was calculated in per-patient and per-test analyses in a large cohort of patients at high risk for IA from 2 North American centers. A total of 272 serum samples obtained from 46 patients with IA and 3005 serum samples obtained from 269 control patients were analyzed using multiple index cutoff values to define positivity.

Results. Per-patient calculations yielded sensitivities of 43% and 70% using index cutoff values of 1.5 and 0.5, respectively; specificity decreased from 93% with use of the 1.5 index cutoff to 70% with use of the 0.5 index cutoff. Per-test calculations yielded sensitivities of 31% and 59% and specificities of 99% and 92% using index cutoff values of 1.5 and 0.5, respectively. Receipt of mold-active antifungal drugs on the day of testing decreased sensitivity; samples obtained from patients not receiving prophylactic or empirical antifungal drugs yielded a sensitivity of 89% and a specificity of 92% (with use of an index cutoff value of 0.5).

Conclusions. These findings have direct implications for preventive strategies, because the diagnostic utility of the antigen assay is compromised during receipt of prophylactic or empirical antifungal therapies.

Girmenia et al: GM testi küf etkili antifungal frofilaksi alanlarda hala pozitifliğini koruyor

Table 1. Microbiological diagnosis in patients with invasive aspergillosis in recent controlled trials of antifungal prophylaxis according to anti-mold activity of the antifungal drug.

Author (reference), type of study	Antifungal drugs; population	Mold active prophylaxis			No mould active prophylaxis		
		Total cases of IA	N (%) with only positive GM assay	N. (%) with *Aspergillus spp.* Isolation	Total cases of IA	N. (%) with only positive GM assay	N. (%) with *Aspergillus spp.* Isolation
Cornely,[3] randomized	Posaconazole *vs.* fluconazole or itraconazole; acute myelogenous leukemia or myelodysplastic syndrome*	7	6 (86)	1 (14)	15	12 (80)	3 (20)
Ullmann,[4] randomized	Posaconazole *vs.* fluconazole; allogeneic stem cell transplant with severe graft-*versus*-host disease	3	3 (100)	0	17	4 (24)	13 (76)
Girmenia,[5] retrospective, historical control	Posaconazole *vs.* topical polyene; acute myelogenous leukemia	15	13 (87)	2 (13)	25	19 (76)	6 (24)
Vehreschild[6] retrospective, historical control	Posaconazole *vs.* topical polyene; acute myelogenous leukemia	2	2(100)	0	11	11(100)	0
	Total	27	24 (89)	3 (11)	68	46 (68)	22 (32)

*itraconazole was included in the group of mold active prophylaxis.

Girmenia C, Hematologica, 2012;97(3):325-7

MAJOR ARTICLE

Serum Galactomannan–Based Early Detection of Invasive Aspergillosis in Hematology Patients Receiving Effective Antimold Prophylaxis

Rafael F. Duarte,[1] Isabel Sánchez-Ortega,[1] Isabel Cuesta,[2] Montserrat Aman,[1] Beatriz Patiño,[1] Alberto Fernández de Sevilla,[1] Carlota Gudiol,[1] Josefina Ayats,[3] and Manuel Cuenca-Estrella[2]

[1]Department of Hematology, Catalan Institute of Oncology, Hospital Duran i Reynals, Barcelona, [2]Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, and [3]Department of Microbiology, Hospital Universitario de Bellvitge, Barcelona, Spain

- **Küf etkili profilaksi alanlarda İFİ riski çok düşük olduğundan GM test genelde negatif ya da yalancı pozitif**
- **Antifungal profilaksi hastalarında galaktomannan testinin klinik şüphe varlığında bakılması daha anlamlı görünüyor**

Duarte RF, CID, 2014

Table 5. Performance of the Serum Galactomannan Assay in High-Risk Patients Receiving Effective Antimold Prophylaxis

Evaluable episodes[a], No.	217
GM test results[b]	
True positive, No. (%)	5 (2.3)
True negative, No. (%)	182 (83.9)
False positive, No. (%)	30 (13.8)
False negative	. . .
Sensitivity, %	100[c]
Specificity, %	85.5[c]
Scenario 1: GM screening of all cases[e]	
Negative predictive value, %	100[c]
Positive predictive value, %	11.8[c]
Scenario 2: Diagnosis of IFD suspicion only[f]	
Negative predictive value, %	100[c]
Positive predictive value, %	89.6[c]

Duarte RF, CID, 2014

İnvazif Aspergilloz Birinci Basamak Tedavi

Drugs	IDSA[1]	UK[2]	ATS[6]	ECIL[3]	DGHO[4]	Australia[5]
AmB DC	D	D		D	EII	Alternative
AmB-LS	AI	AI	AI	BI	AII	Alternative
ABLC				BII		
ABCD				D		
Itraconazole				CIII		
Posaconazole						
Voriconazole	AI	AI	**AI**	AI	AI	Recommended
Caspofungin		AI*		CII		
Micafungin						
Combination	Not recommended	Discouraged		Discouraged	CIII	No supportive evidence

***Caspofungin graded AI for empirical therapy only in BCSH guidelines**

1. Walsh TJ, et al. Clin Infect Dis 2008;46:327–60.
2. Prentice AG, et al. http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf
3. Maertens J et al. Bone Marrow Transplantation 2011; 46:709–18
4. Bohme A et al. Ann Hematol 2009;88:97–110
5. Thursky KA, et al. Intern Med J 2008;38:496–520. 6. Andrew H, Am J Respir Crit Care Med Vol 183, 2010

Invasive aspergillosis: First-line

Agent	Grade	Comments
Voriconazole	A I	2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)
Ambisome	B I	dose 3 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C II	
Itraconazole	C III	
ABCD	C I	
Combination voriconazole + anidulafungin	C I [1]	
Other combinations	C III	
AGAINST THE USE		
Amphotericin B deoxycholate	A I	

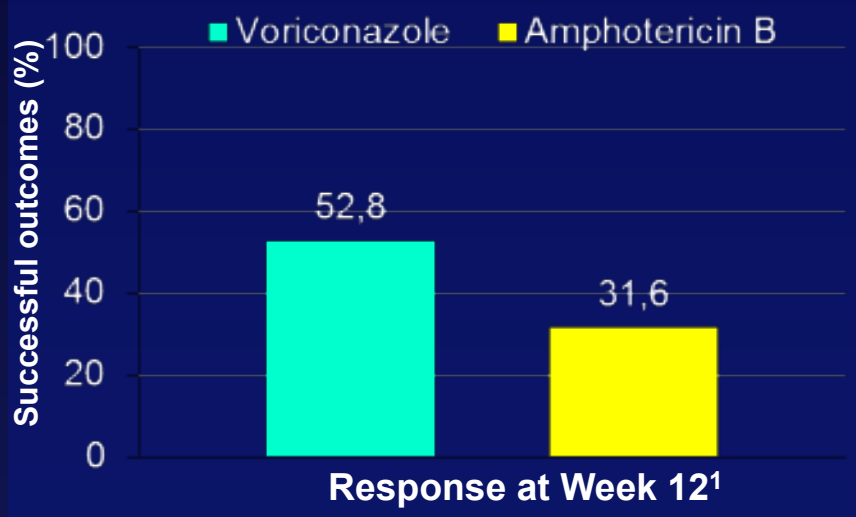
[1] *provisional*

In the absence of data in 1st line, posaconazole has not been graded

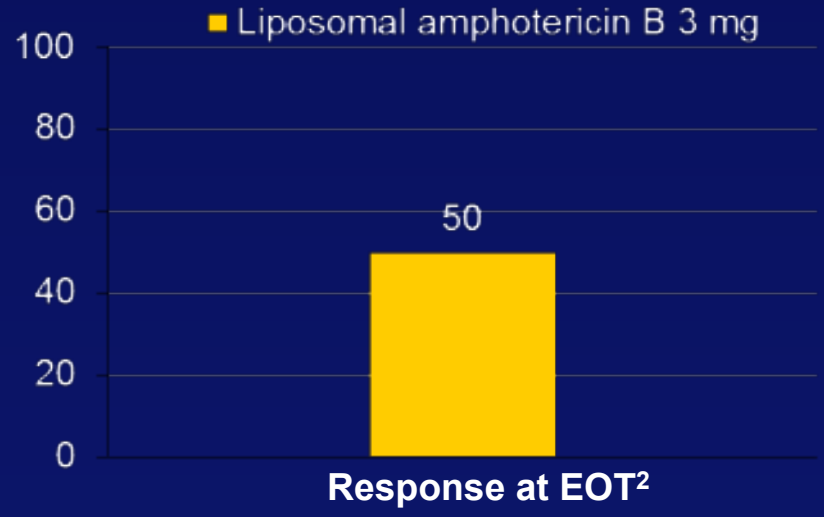
Invasive aspergillosis: salvage

Agent	Grade	Comments
Ambisome	~~B III~~ B II	no data in voriconazole failure
ABLC	~~B III~~ B II	no data in voriconazole failure
Caspofungin	B II	no data in voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line
Combination	~~C II~~ B II	different studies, not randomized

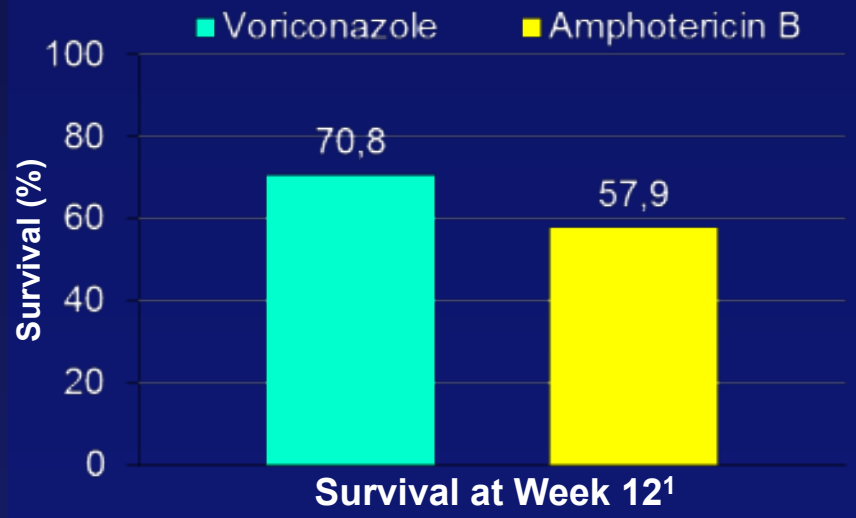
İnvaziz Aspergilloz Tedavisi



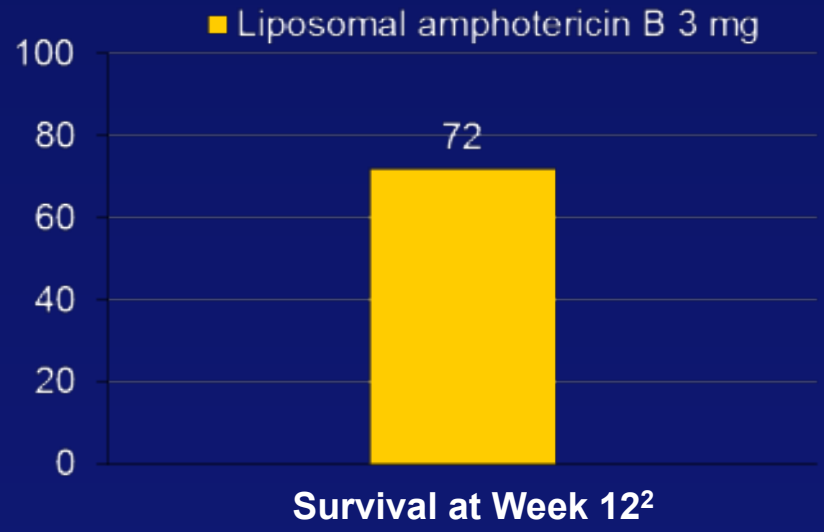
Response at Week 12[1]



Response at EOT[2]



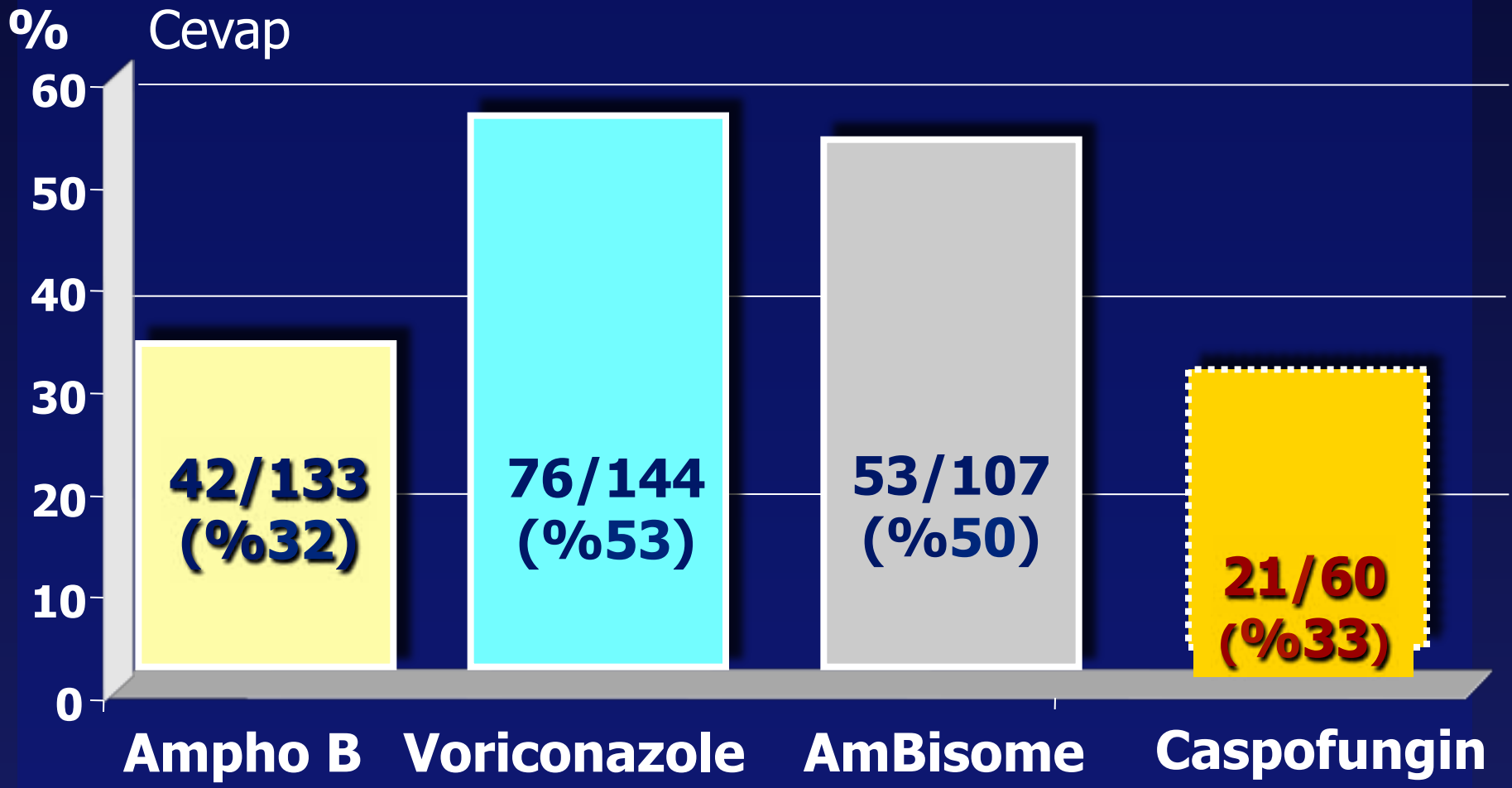
Survival at Week 12[1]



Survival at Week 12[2]

1. Herbrecht R et al. N Engl J Med 2002;347:408–15; 2. Cornely OA et al Clin Infect Dis 2007;44:1289–97.

Invazif Aspergilloz'un primer tedavisi



Herbrecht et al N Engl J Med 2002; 347:408-415
Cornely et al. Blood 2005; 106:900a, Abstract 3222
Candoni et al. Eur J Haematol 2005; 75:227-233

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

- İzavukonazol İFİ tedavisinde en az vorikonazol kadar başarılı (non-inferior)
- Primer İFİ tedavisinde kullanılabilir
- Daha az hepatotoksisite, göz ve cilt bulguları
- IV form (siklodekstrin içermez), oral form

Maertens J, Lancet 2016

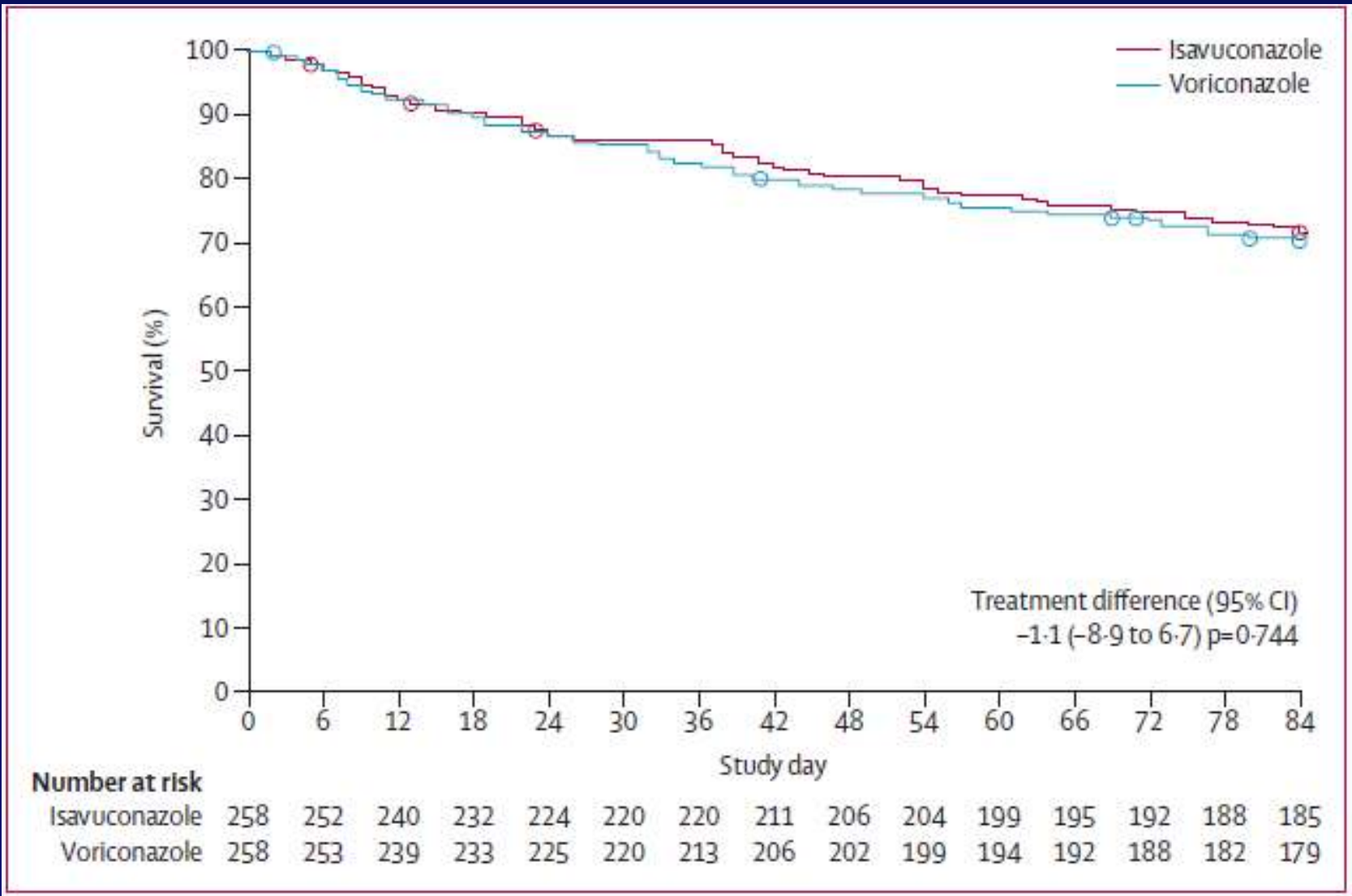


Figure 2: **Survival from first dose of study drug to day 84**

Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Tedavi Takibi
Hangi sıklıkta CT çekmeli?

Table 4. Investigations in both the empirical and the diagnostic-driven pathway

Investigation	Timelines and comments
Diagnostic investigations	
chest CT (preferably volume acquisition with thin slice reconstruction)	initial persistent fever
	repeat frequency no sooner than 2 weeks, unless significant clinical deterioration
CT/MRI other sites	according to clinical features
biopsy	according to clinical features
	every attempt should be made to obtain tissue (allows proven diagnosis to be made)
	detection of galactomannan has been used as a criterion for starting therapy
whole-blood PCR	pre-therapy and throughout the risk period
	twice weekly during admission
	data suggest that some PCR tests can help exclude aspergillosis and candidosis because of the high negative predictive value
	detection of fungal nucleic acid might be useful as a criterion for starting therapy
	efforts are under way to define a standard for *Aspergillus* PCR
serum β-D-glucan	pre-therapy and throughout the risk period
	twice weekly during admission
	might help exclude aspergillosis and candidosis because of the high negative predictive value
	detection of β-D-glucan might be useful as a criterion for starting therapy

Aksi bir klinik gelişme olmadıkça aspergilloz tanısı ile izlenen hastada takip amaçlı **2 haftadan önce** tomoğrafi çekmeye gerek yoktur

Agrawal S,Et al.JAC 2011;66 (suppl.1):i45

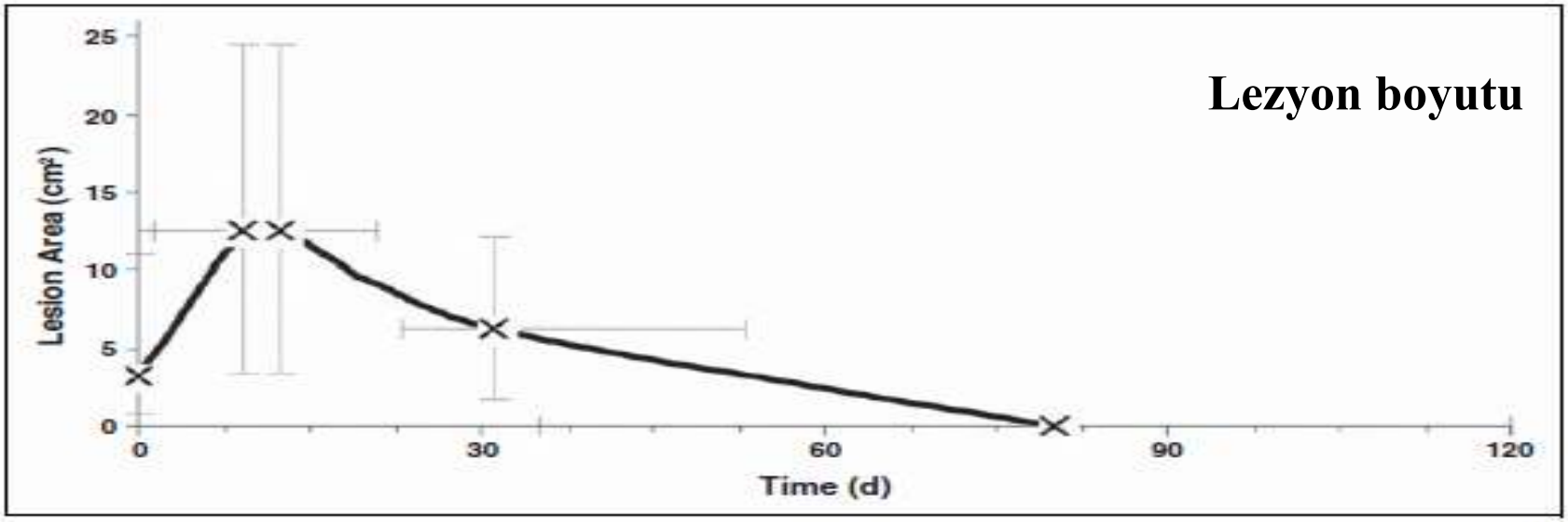
İnvazif aspergillozda tedavinin başarılı kabul edilebilmesi için radyolojik görüntülemede en az yüzde kaçlık gerileme olması beklenir?

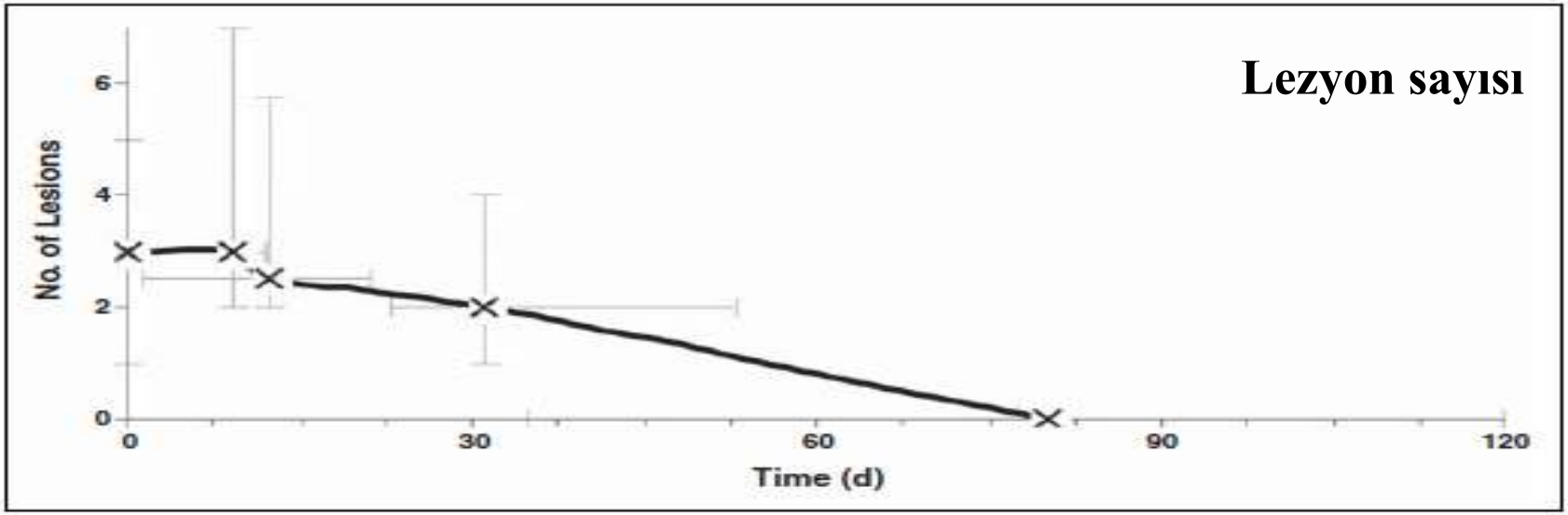
A. %75
B. %50
C. %25
D. %10
E. Radyolojik görüntü ile tedavi başarısı değerlendirilmez

İnvazif Aspergillozda Tedaviye Yanıtı Değerlendirme

İnvazif Aspergillozda Tedaviye Yanıt Değerlendirmesi
Başarılı
Tam başarı: Semptom ve şikayetlerin tamamen kaybolması ile birlikte radyolojik bulguların da tamamen düzelmesi ya da sekel /skar kalması **Kısmi Başarı**: Semtom ve şikayetleride gerileme ile birlikte radyolojik bulgularda **en az %25 gerileme olması**
Başarısız
Stabil yanıt: Semtom ve şikayetlerde hafif düzelme ya da hiç düzelme olmaması ve radyllojik görüntülemede **< %25 gerileme** **Progresyon**: Semtom ve şikayetlerde artış olması ile birlikte radyolojik lezyonlarda ilerleme, yeni lezyonların eklenmesi ve kültürlerde üremelerin devamlılık göstermesi

Nodül kinetiği





Brodefel et al ,AJR 2006

Nodül Boyutu: Tedavi başarısı / başarısızlığı

- Nötrofil: 0/µL GM serum: 3.2 GM BAL: 8.6
- Nötrofil: 12.360 /µL GM serum: 0.8 GM BAL: 1.2

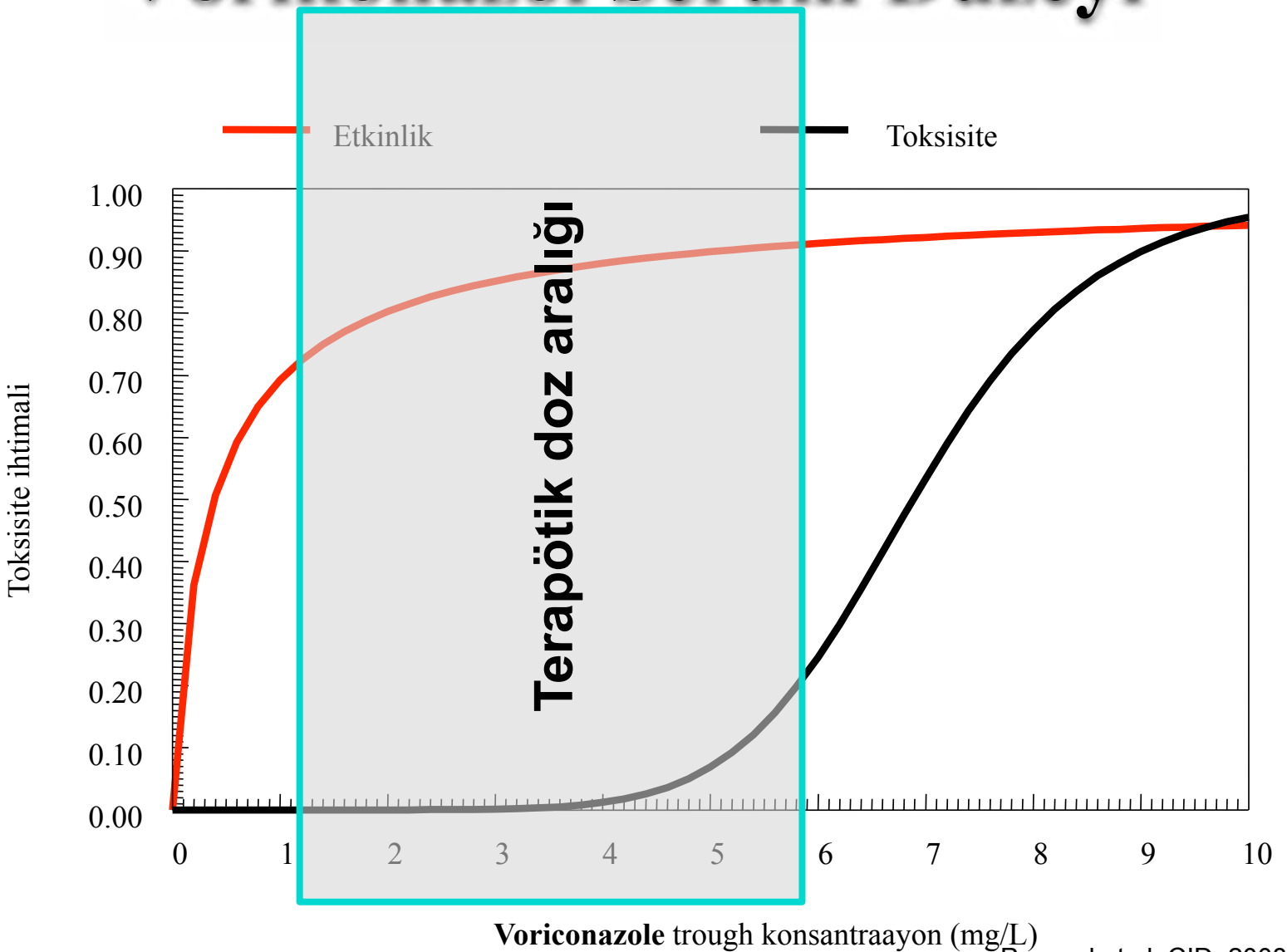
Tedavinin erken döneminde <u>bazen</u> nodül boyutlarında artış görülebilir

Caillot et al. J Clin Oncol 2001; 19: 253-9

Vorikonazol Tedavisinde Dikkat Edilmesi Gereken Durumlar

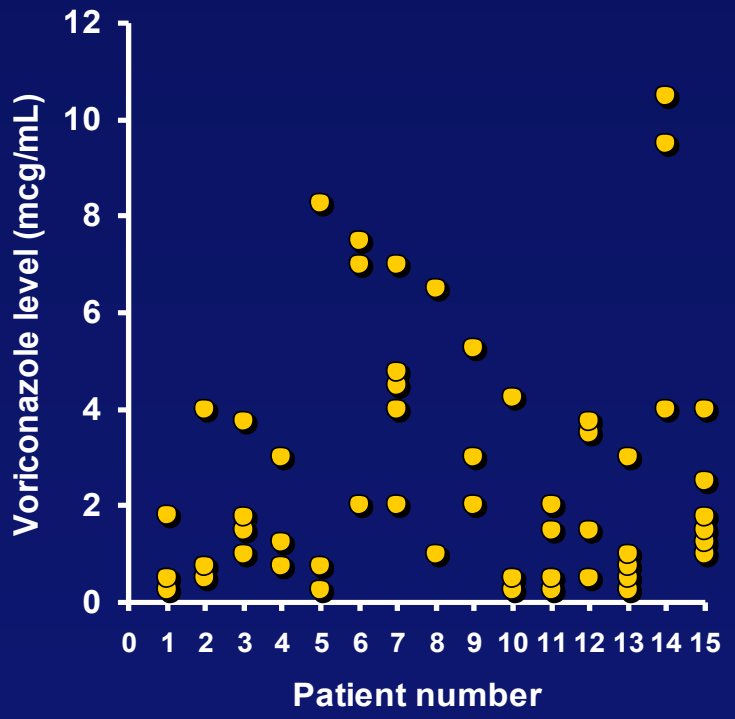
- İlaç etkileşimleri
- Yan etkiler:
  - Hepatotoksisite (%15)
  - **Fotopsi** sık görülür
  - Halüsinasyonlar, döküntü
- IV formu: siklodekstrin içerir: renal doz ayarlaması
- Breakthrough fungal enfeksiyonlar: *Mucorales*
- Terapötik doz monütörizasyonu

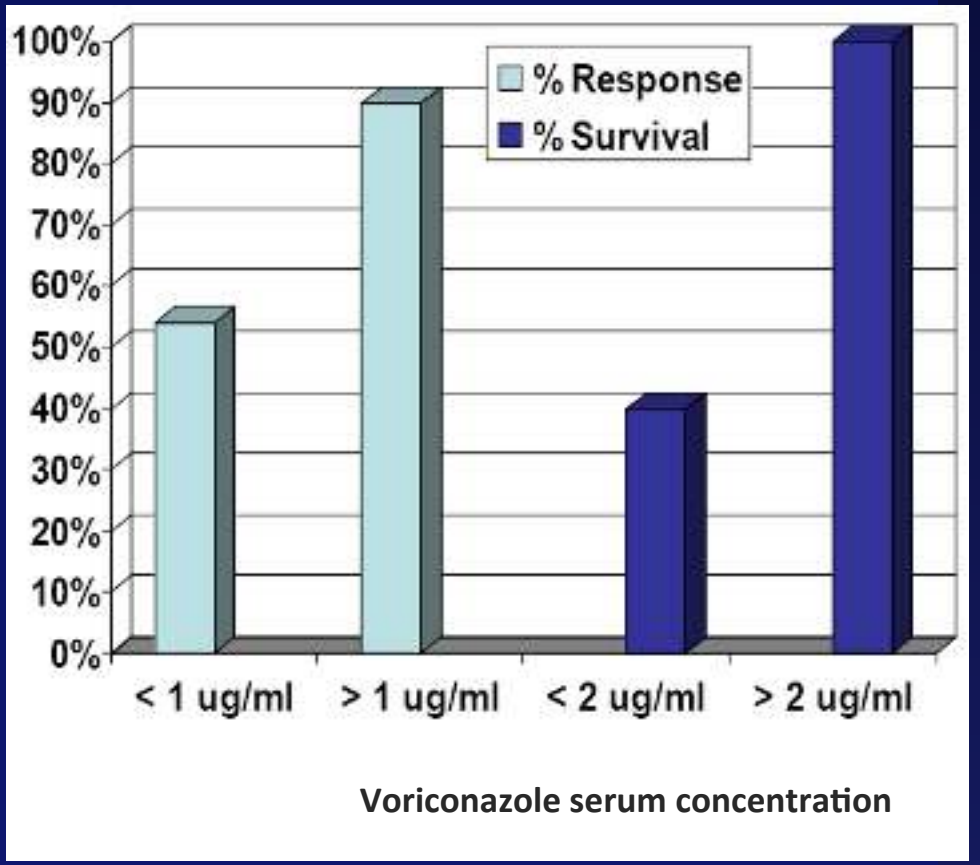
Vorikonazol Serum Düzeyi



Pascual et al. CID. 2008. 46:201-11

Voriconazole TDM: Serum düzeyi ve tedavi başarısı

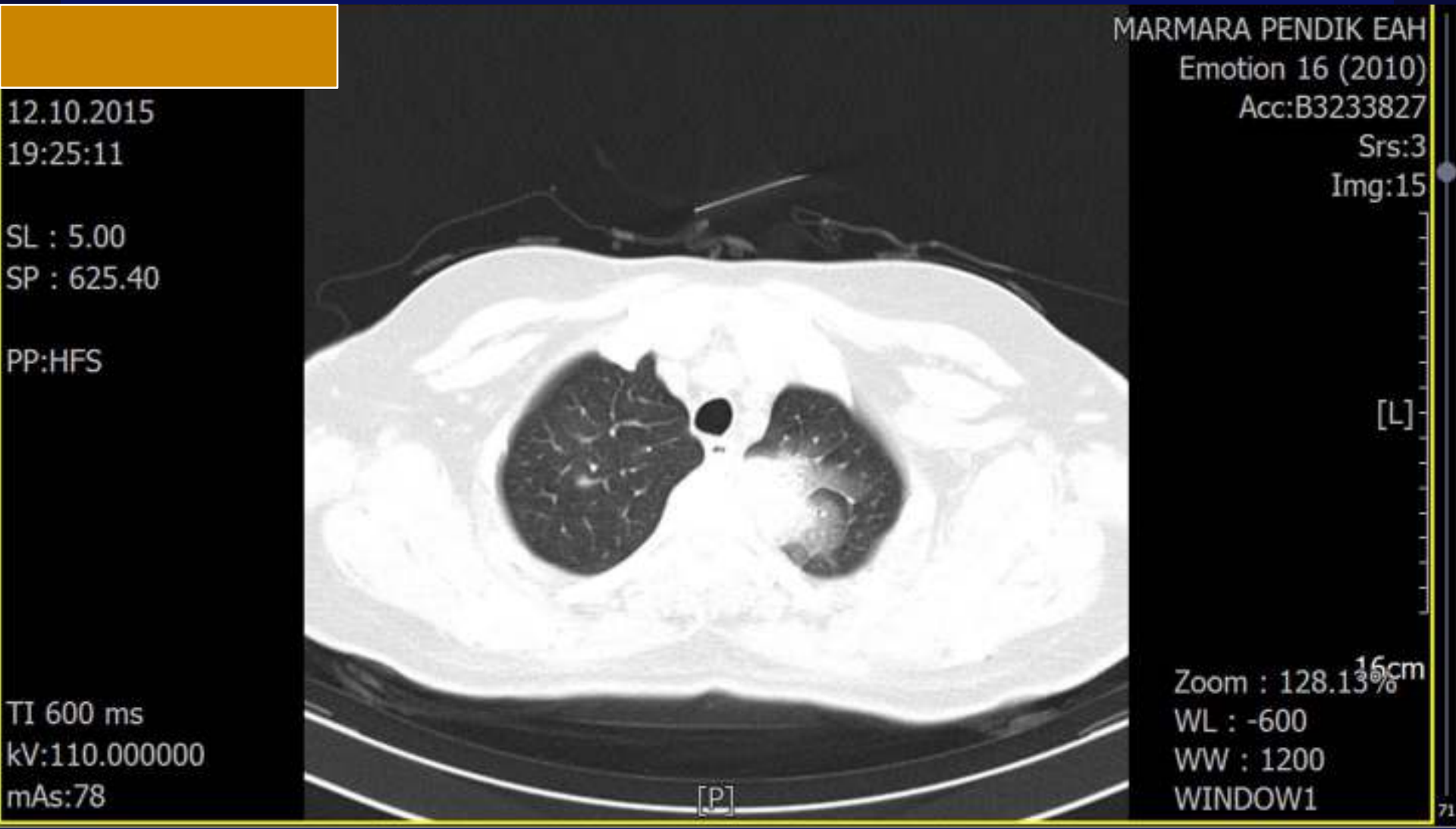




Trifilio S et al. *Cancer* 2007; 109: 1532-5.
Andes D. ICAAC workshop 2010
Pascual at al Clin Infec Dis 2008;46:201
Smith J et al. *Antimicrob Ag Chemother*. 2006; 50:1570-1572

Vaka

- Posakonazol profilaksisi altında ateşi çıkan hasta
- AML – indüksiyon kemoterapisi
- Piperacillin tazobacatam almakta
- Serum galaktomannan öncekiler negatif, yeniden gönderildi
- İlk ateş atağındaki tomografileri normal
- Toraks CT istendi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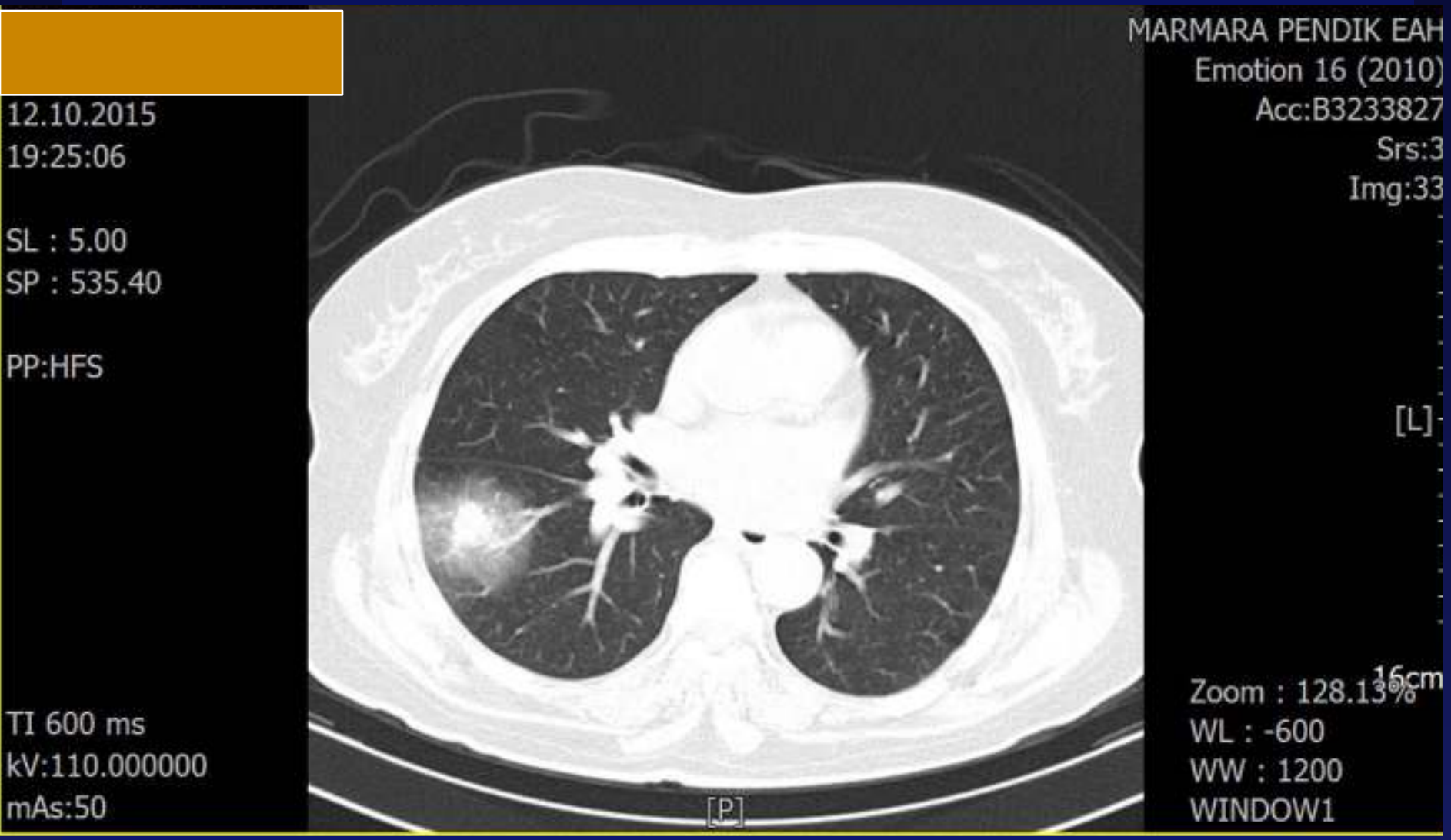
12.10.2015
19:25:11
SL : 5.00
SP : 625.40
PP:HFS
[L]
16cm
Zoom : 128.13%
WL : -600
WW : 1200
WINDOW1
TI 600 ms
kV:110.000000
mAs:78
[P]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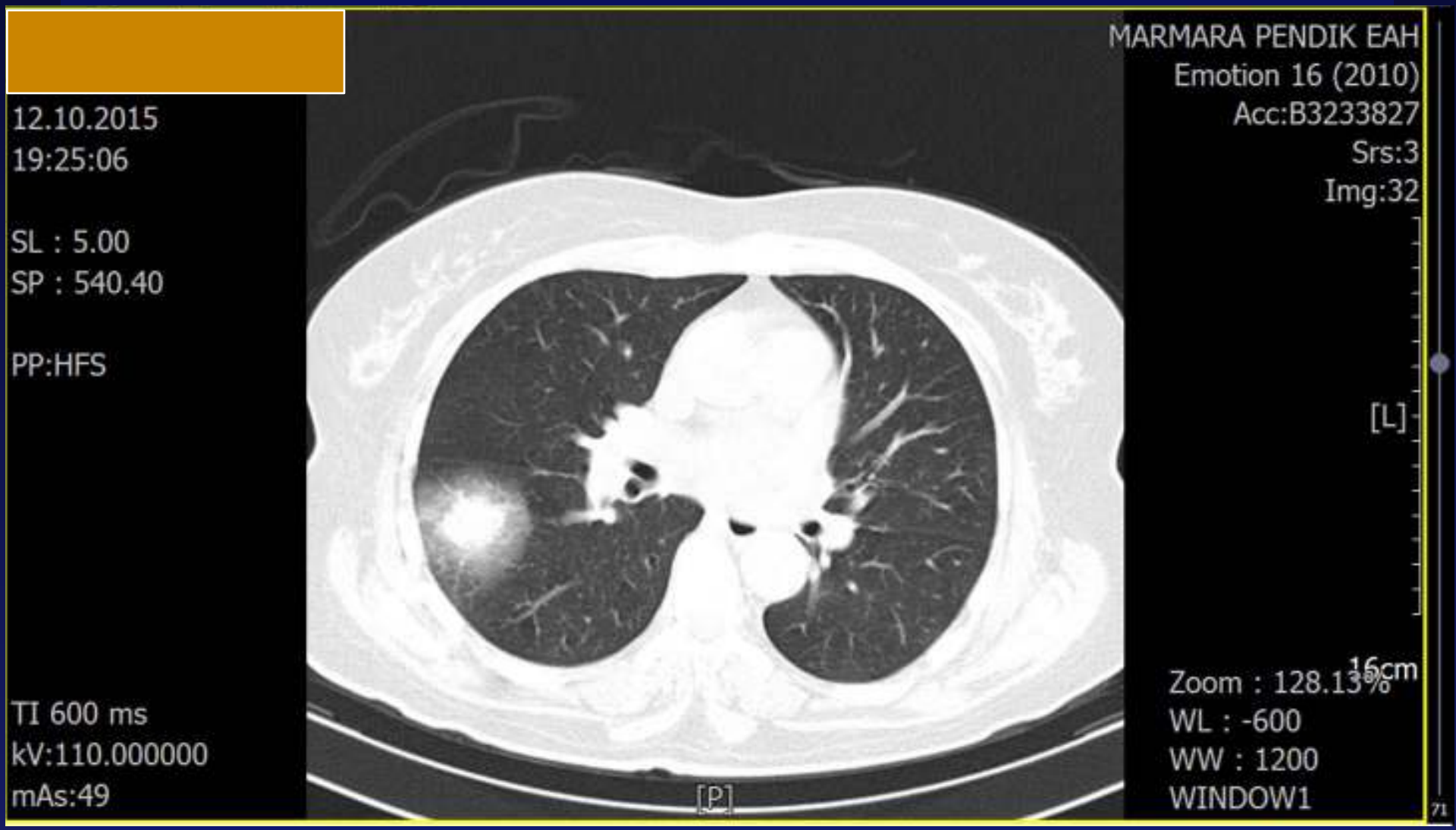
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Emotion 16 (2010)
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16cm
Zoom : 128.13%
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WW : 1200
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En uygun tedavi yaklaşı

A. Serum ve mümkünse BAL galaktomannan antijen testini gönderip **posakonazol** dozunu yükseltirim
B. Serum ve mümkünse BAL galaktomannan antijen testini gönderip empirik **vorikonazol** başlarım
C. Serum ve mümkünse BAL galaktomannan antijen testini gönderip empirik **lipozomal AmB** başlarım

Posakonazol TDM – ECIL 5

- **Posakonazol profilaksisinde 5. gün genelde düzey bakılması önerilir**
- **Diğer:**
  - Etkileşen ilaç ile kullanımında (proton pompa inhibitörü)
  - Besinlerle alınamaması durumunda
  - Eşlik eden ishal ve intestinal GVHH varlığında
  - Profilaksi altında yeni İFİ gelişmesi
    - **Düzey düşükse aspergilloz tedavisinde vorikonazol verilebilir**

Summary of TDM plasma target level recommendations

Triazole	Recommended plasma range[a]	SOR	Timing of first trough sample
Voriconazole	Prophylaxis and treatment: Acceptable: 1-6 mg/L; Optimal: 2-5 mg/L	AII (efficacy) AII (toxicity)	After 2-5 days; (repeat sampling recommended)
Posaconazole	Prophylaxis: > 0.7 mg/L Treatment: > 1.0 mg/L	BII (efficacy) AII (efficacy)	Tablet/IV: after 3 days: Suspension: 5-7 days.*
Itraconazole	Prophylaxis: 0.5-4 mg/L Treatment: 1-4 mg/L	AII (efficacy) BII (toxicity)	7-15 days;*

[a] values from a chromatography assay: i.e. high performance liquid chromatography (HPLC), liquid chromatography mass spectroscopy (LC/MS) of LC/MS/MS

[b] patients without symptoms of clinical toxicity may not warrent dosage adjustment, decisions should be individualised to the patient

[c] higher troughs (≥ 2) are advocated for severe infections or treatment of pathogens with potentially or documented elevated MICs (around 1 mg/L or higher)

*earlier sampling possible and may be desirable during treatment.

* Earlier sampling possible using lower targets

ECIL-5 (2013)

Mucormycosis
Recommendation for first line (part 1)

Management includes antifungal therapy, control of underlying conditions and surgery	**A II**
Antifungal therapy	
- AmB deoxycholate	C II
- Liposomal AmB	B II [1]
- ABLC	B II [1]
- ABCD	C II
- Posaconazole	CIII[2]
- Combination therapy	CIII

[1] Liposomal amphotericin B should be preferred in CNS infection and/or renal failure.

[2] No data to support its use as first line treatment. May be used as an alternative when amphotericin B is absolutely contraindicated.

Mucormycosis
Recommendation for first line (part 2)

Management includes antifungal therapy, control of underlying conditions and surgery.	A II
Control of underlying condition	A II [3]
Surgery	
- rhino-orbito-cerebral	A II
- soft tissue	A II
- localized pulmonary lesion	B III
- disseminated	CIII[4]
Hyperbaric oxygen	CIII

[3] Control of underlying condition includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy

[4] Surgery should be considered on a case by case basis, using a multi-disciplinary approach

Mucormycosis
Recommendation for salvage therapy (failure of first line)

Salvage (failure of first line)

Management includes antifungal therapy, control of underlying disease and surgery.	A II
Posaconazole	BII
Combination lipid AmB and caspofungin	~~BII~~ B III
Combination lipid AmB and posaconazole	~~CIII~~ B III

AGAINST THE USE

Combination with deferasirox	A II

Mucormycosis
Recommendation for maintenance therapy or in case of intolerance to first line therapy

Maintenance therapy (prior response or stable disease)

Or intolerance to first line therapy

Posaconazole	B II [1]

[1] whenever possible, overlap of a few days (at least 5) with first line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated

İnvazif Fusarium Enfeksiyonlarının Tedavisi

- Sadece immün kompromize kişilerde gelişir
  - Normal insanlarda onikomikoz, keratit
- *Fusarium solani* en sık görülen etkendir
- Kan kültüründe üreme ile tespit edilebilir
- Tedavide
  - Lipit formülasyonlu AmB
  - Vorikonazol
  - Gerekirse kombinasyon tedavisi
- Nötropeni sürdüğü müddetçe mortalite çok yüksektir


TEŞEKKÜRLER