Hematolog Gözüyle Fungal İnfeksiyonlara Yaklaşım

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Nötropenik hastalarda fungal infeksiyonlar

İnvaziv Candidiasis (ve diğer maya mantarları) için yüksek risk:

- HKHN hazırlık rejimi sonrası ilk 3 hafta
- Yüksek doz ara-C
- Tedavi ilişkili ciddi Gİ zararlanması
- Nötropeni döneminde 1'den fazla alanda mayalar ile kolonizasyon

Düşük risk: (< %2)

- Yüksek risk özelliklerinin olmaması
- Santral venöz katater olmaması

İnvaziv aspergillosis (ve diğer küf mantarları) için yüksek risk:

- Allojeneik HKHN+graft yetmezliği
  - (>21 gün nötrofil <200/mm3)
- AML, MDS veya ALL için yoğun kemoterapi
  - (>21 gün nötrofil <200/mm3)
- Nötrofil<200/mm3 + steroid tedavisi
- Önceki nötropeni döneminde invaziv aspergillosis
- Çevrede yüksek yoğunlukta fungal sporların varlığı

Düşük risk:

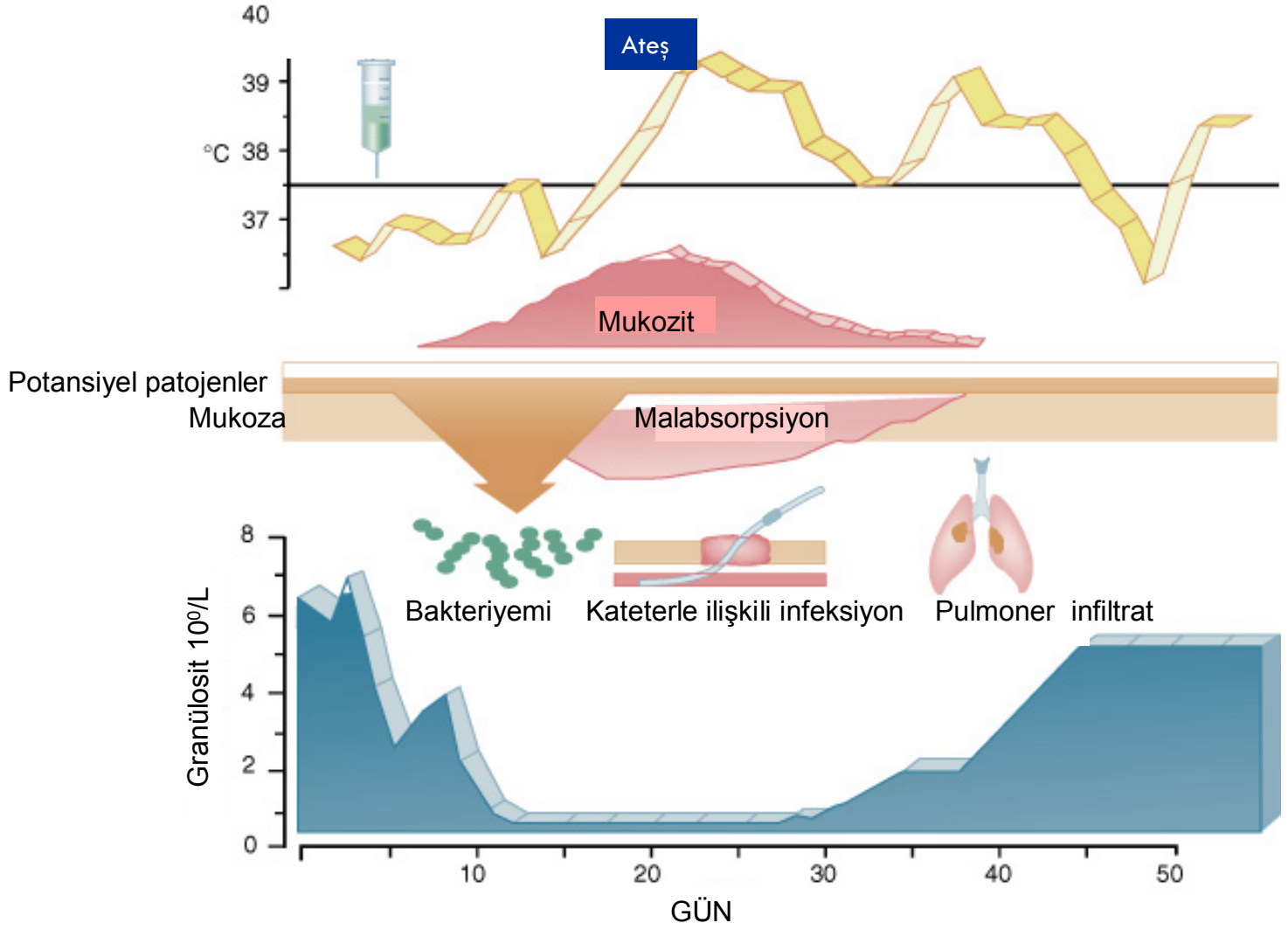
- Standart Otolog HKHN
- Yüksek risk özelliklerinin olmaması

Ek risk faktörleri:

- Deri ve mukoza bütünlüğünün bozulması
  - Yüksek doz kemoterapi ilişkili mukozit
  - IV girişimler
  - Santral venöz kateter uygulaması
  - Diğer kateterizasyonlar
- Monosit/makrofaj sisteminde yetersizlik
  - Altta yatan hastalık
  - Kemoterapi
  - Kortikosteroid uygulaması
- Hücresel bağışıklıkta yetersizlik
- Humoral bağışıklıkta yetersizlik

KANSER HASTALARINDA ÖLÜM NEDENLERİ

ÖLÜM NEDENİ	%
Bakteri veya Mantar İnfeksiyonu	35
Kanama ve infeksiyon bulguları	27
Diğer (çoğu metabolik)	20
Kanserin ilerlemesi	18



KEMOTERAPİ SÜRECİNDE OLUŞAN OLAYLAR

Altta yatan hastalığın durumu

Table 2. Results of multivariate analysis of 12-week overall mortality for patients with invasive aspergillosis (IA) after stratification by treatment.

Variable	Reference category	Hazard ratio (95% CI)	*P*
Main host factor			
Allogeneic HSCT or SOT	Hematologic malignancy	1.7 (1–2.8)	.045
Other	...	1.6 (0.9–2.8)	
Progression of underlying disease			
Yes	No	4.2 (2.5–7.1)	<.001
Prior noninfectious respiratory disease			
Yes	No	1.7 (1.1–2.5)	.009
Corticosteroid dosage on day 1 of IA			
≥0.2 mg/kg	<0.2 mg/kg	2.4 (1.5–3.9)	<.001
Creatinine clearance level			
30–59 mL/min	≥60 mL/min	1.4 (0.9–2.2)	.007
<30 mL/min	...	2.1 (1.3–3.5)	
Monocyte count			
≤100 cells/μL	>100 cells/μL	1.6 (1.1–2.7)	.015
Site of IA infection			
Disseminated	Lungs only	3.3 (1.8–6.2)	.001
Other single organ	...	NA (NA)	
Extent of pulmonary lesions			
Diffuse lung involvement (≥2 lobes)	Single pulmonary lobe involvement	2.3 (1.4–4.0)	.007
No lesion	...	1.0 (0.1–8.3)	
Pleural effusion			
Present	Absent	1.6 (1.0–2.3)	.030
Degree of certainty of IA diagnosis			
Possible	Proven or probable	0.5 (0.3–0.8)	.001

NOTE. Only statistically significant ($P < .05$) predictors of overall survival are listed. HSCT, hematopoietic stem cell transplantation; NA, not available; SOT, solid-organ transplantation.

Avrupa'da kandidemi

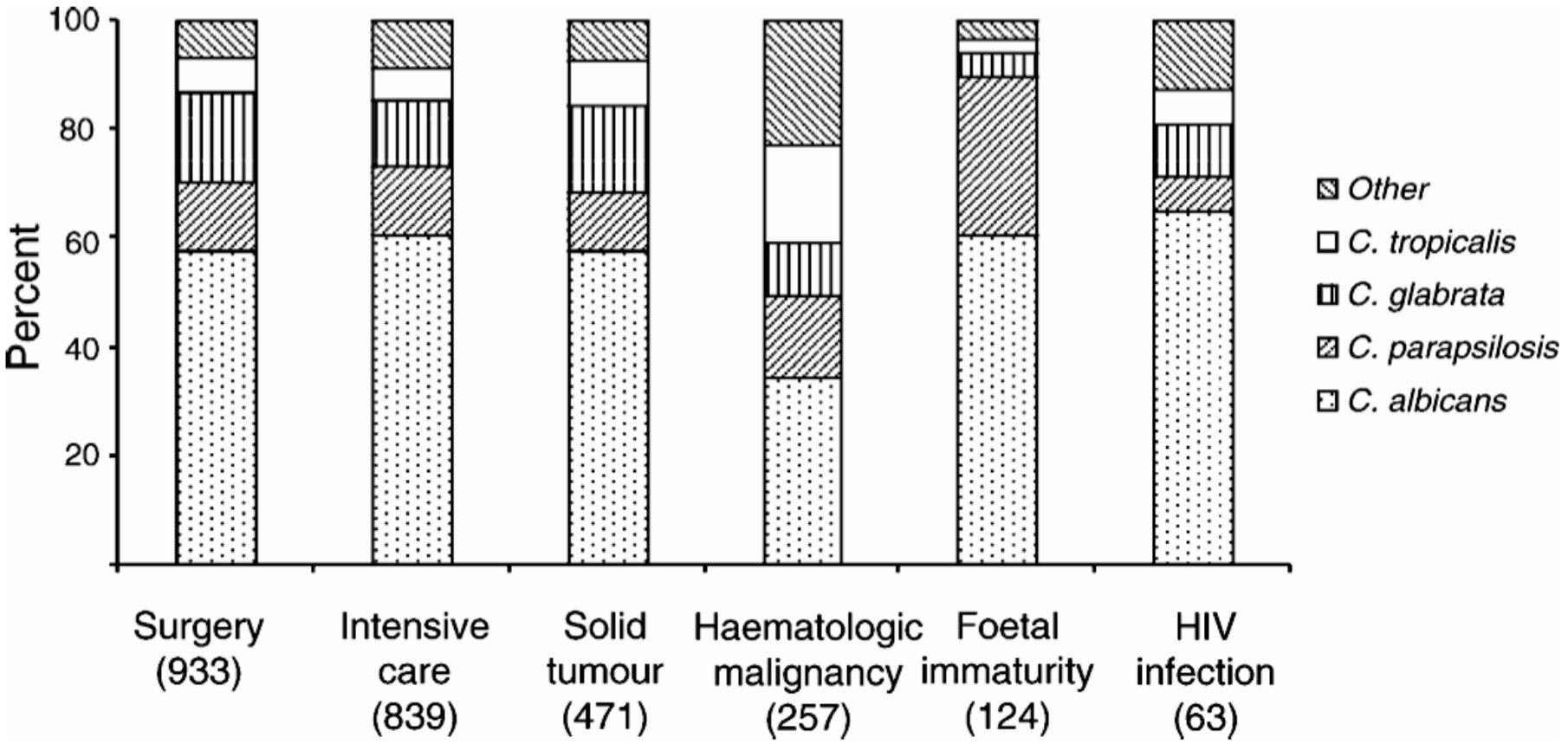
Table 2
Underlying pathology/medical care of patients with candidaemia ($n = 2089$; more than one may be present in each episode)

	No.	%
Surgery	1007	48.2
Intensive care	839	40.2
Solid tumour	471	22.5
Steroids	364	17.4
Haematological malignancy	257	12.3
Premature birth	125	6.0
HIV infection	63	3.0
Burns	29	1.4

Tortorano et al., Int J Antimicrob Agents 2006; 27: 359-366

Avrupa'da Kandidemi

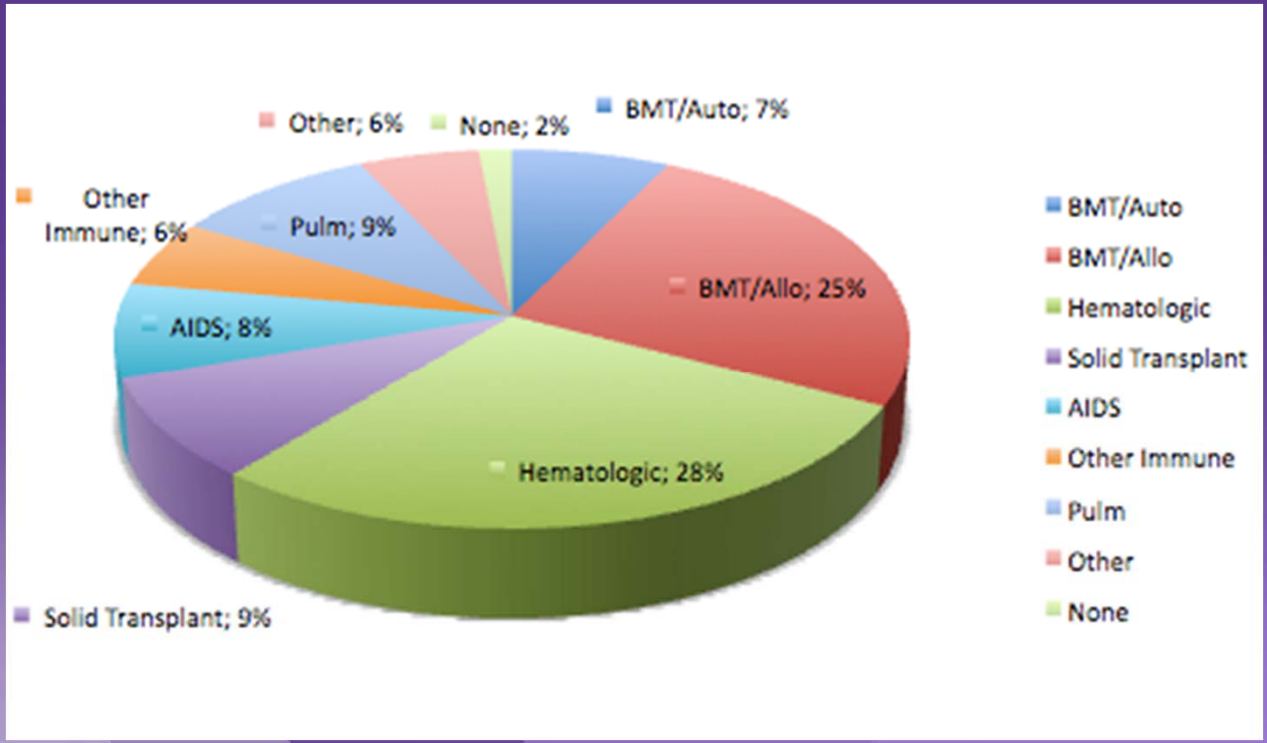
Candida türlerinin dağılımı



Tortorano et al., Int J Antimicrob Agents 2006; 27: 359

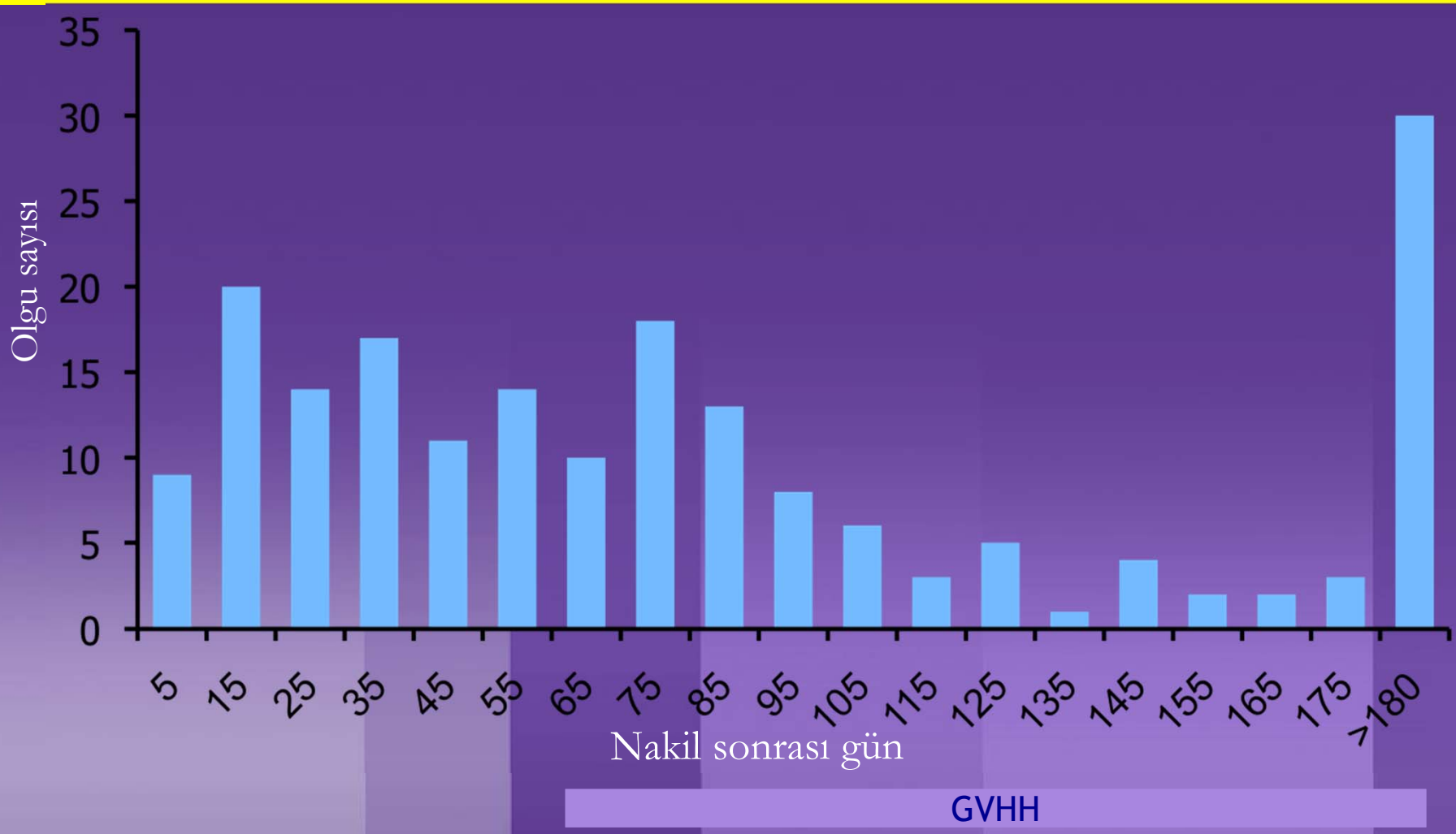
Invaziv Aspergilloz olgularında altta yatan hastalık

595 hasta



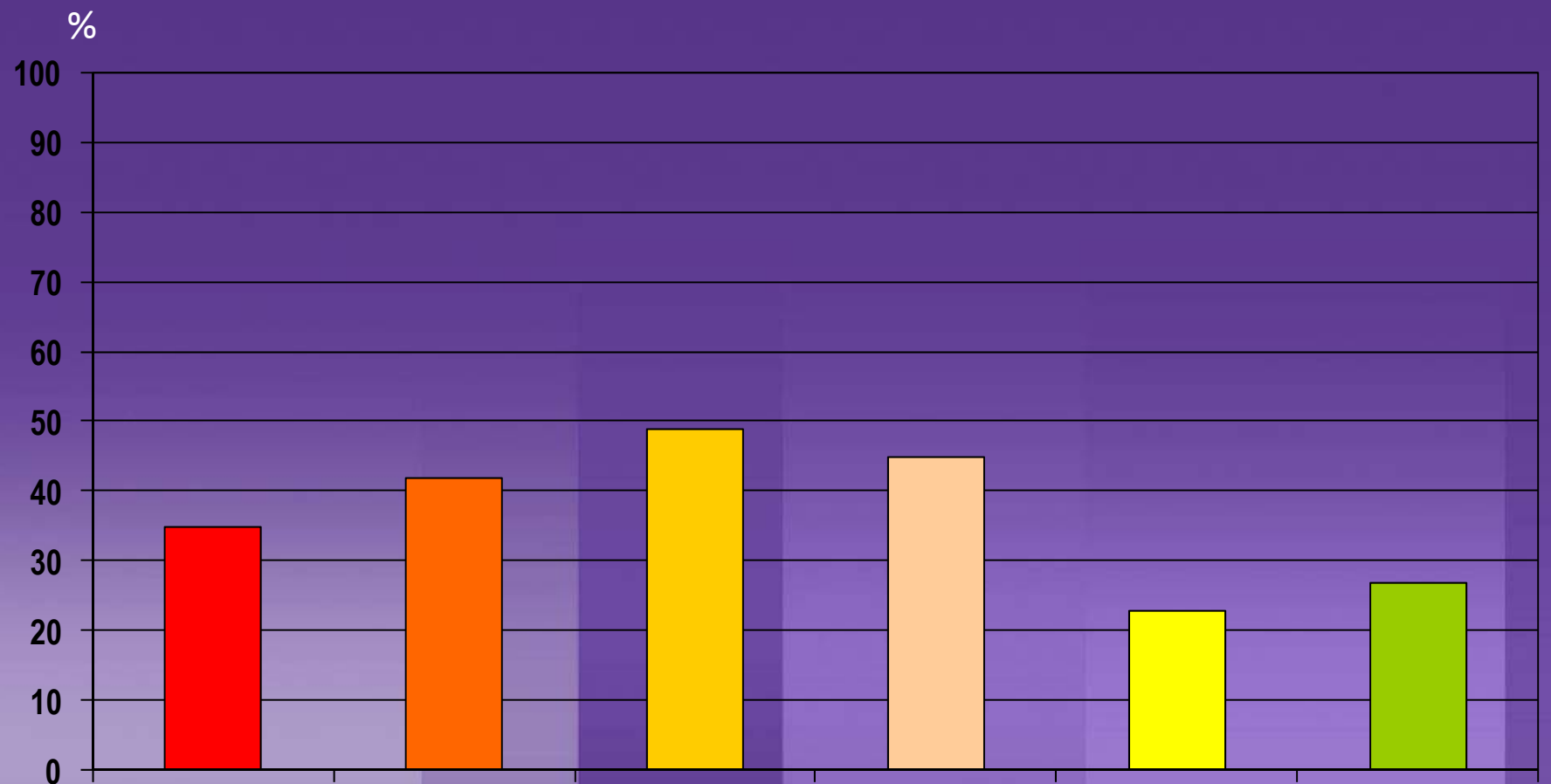
Patterson TF, et al. Medicine, 2000;79:250-60

Allojeneik KHN sonrası Aspergillozis sıklığı, 1993-1998



Marr KA, et al. Blood 2002;100:4358

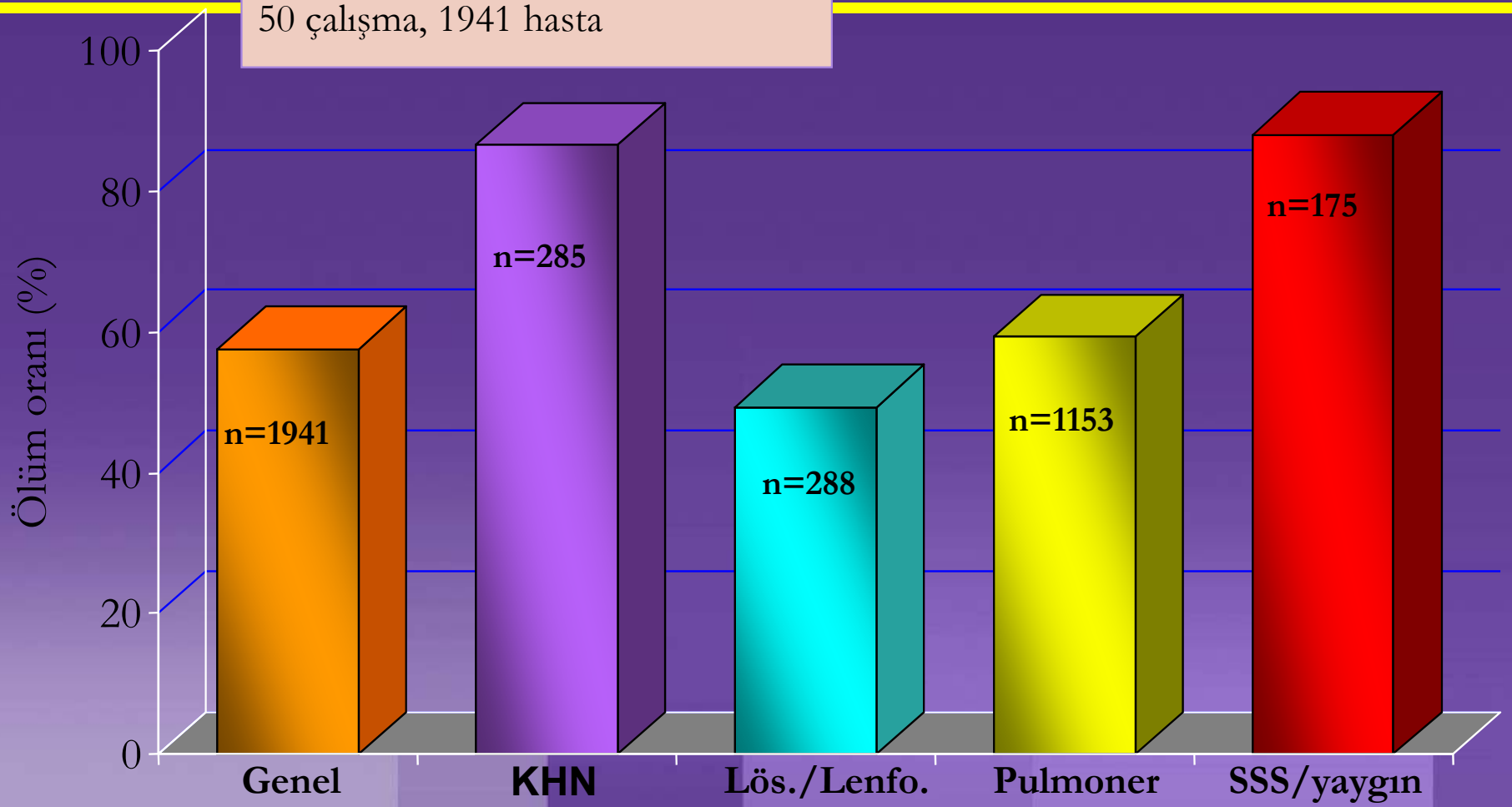
İnvaziv *Candida* enfeksiyonlarına bağlı mortalite



Tortorano et al., EJCMID 2004; 23: 317

Invaziv Aspergilloz ile ölüm, 1995 sonrası

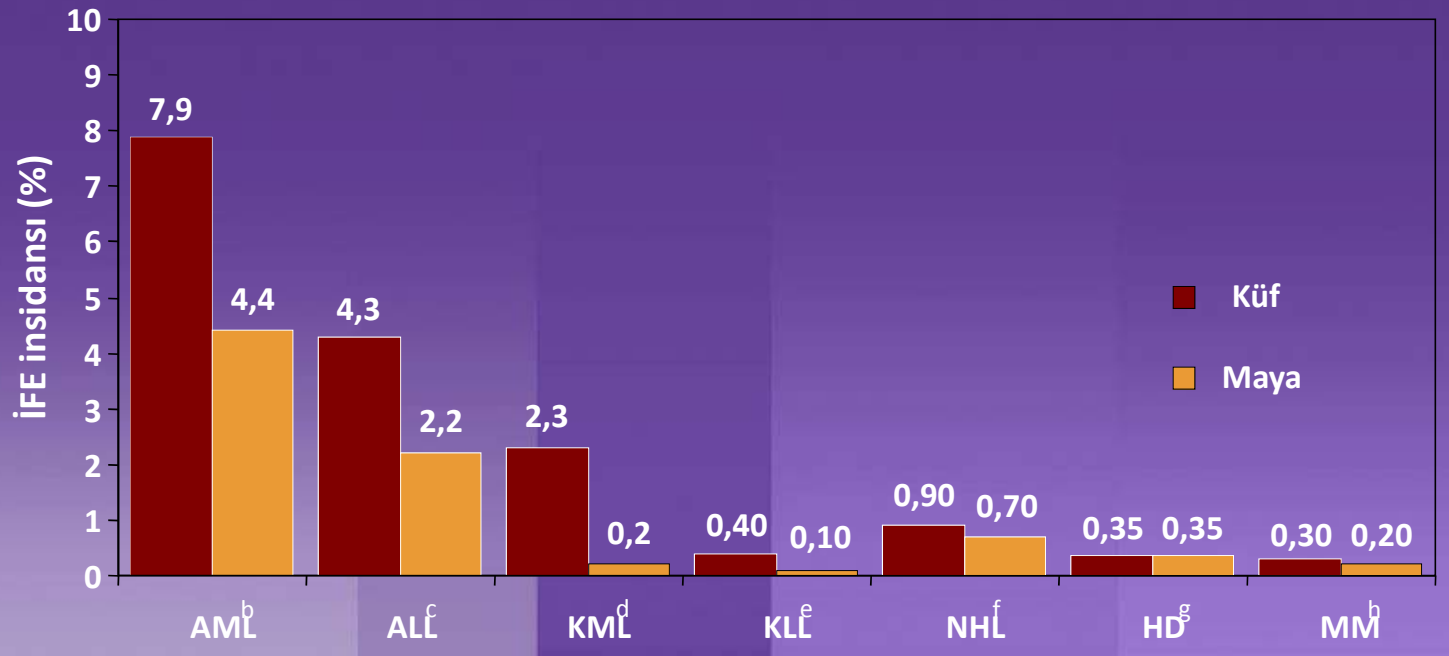
50 çalışma, 1941 hasta



Lin et al. Clin Infect Dis 2001; 32:358.

Farklı Hematolojik Malignite Tiplerine Sahip Hastalarda İFE İnsidansı

- İtalya – 1999 ile 2003 arasında
- 11.802 hastadaki genel insidans **%4,6'ydı**
  - Vakaların **%2,9**'undan küfler, **%1,6**'sından ise mayalar sorumlu tutuldu



Pagano L, et al. Haematologica. 2006;91:1068-1075.

Avrupa'da İnvaziv Fungal İnfeksiyonlar

*(%)	Aspergillus	Fusarium	Zygomycetes	Candida	Trichosporon	Cryptococcus
Genel sıklık	2.6	0.1	0.1	1.5	0.06	0.07
Genel mortalite	42	53	64	33	50	29

** (MDS, aplastik anemi ve KHN hariç*

SIKLIK (%)	Allogeneic KHN (%)	Otolog KHN (%)
Aspergillus	2.8	0.4
Candida	0.9	0.8

Pagano L, Haematologica 2006; 91(8):1068-73

Pagano L, CID 2007:45 (1):1161-1170

MORTALITE (%)	Allogeneic KHN	MR	MMR	MUR	Otolog KHN
Aspergillus	77.2	71	83	74	57.1
Candida	40				43.8
Other	40				-

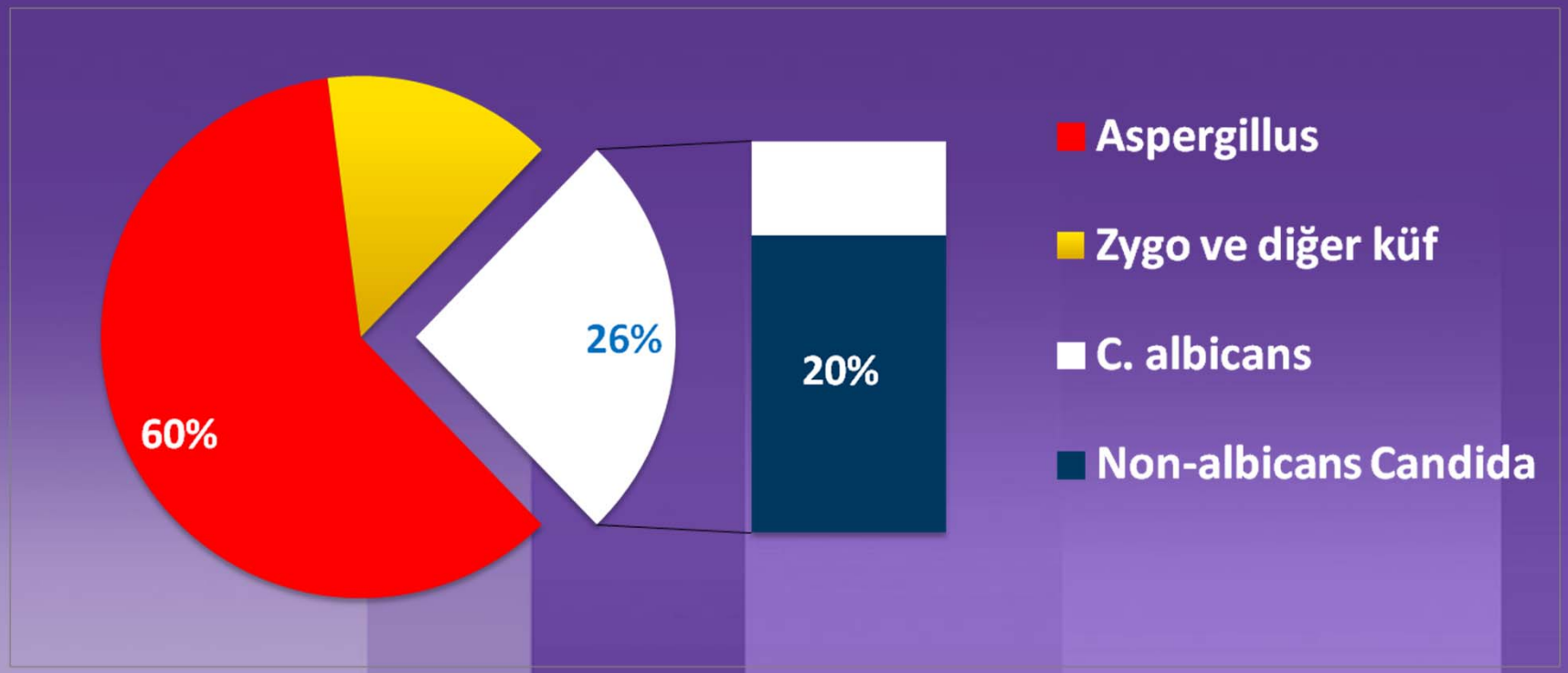
MAYA

- *Candida*
  - *Albicans*
  - *Non albicans*
- Cryptococcus
- Trichosporon
- M.furfur

KÜF

- *Aspergillus*
- Zygomycetes
- Fusarium
- Scedosporium
- Sporothrix schenckii

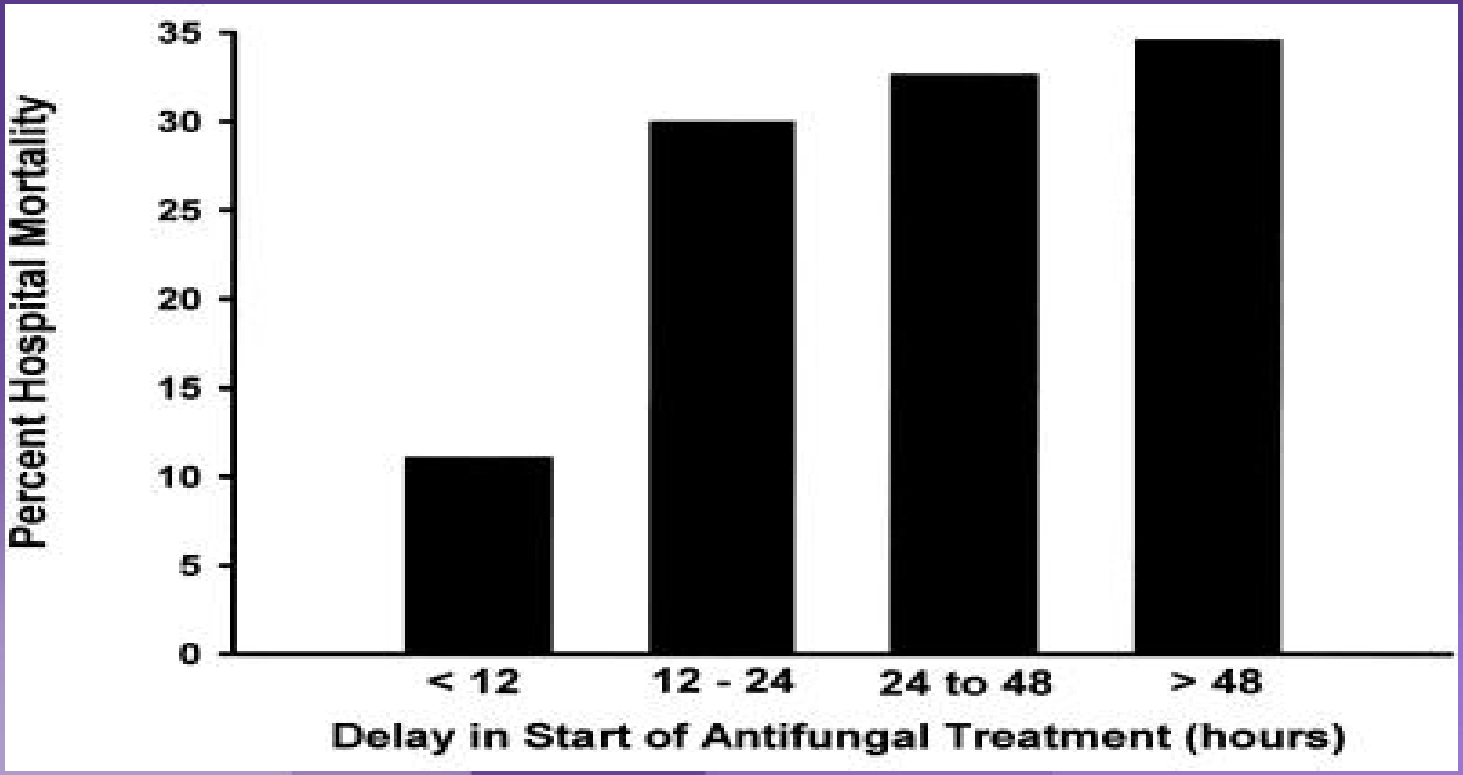
İnvaziv Fungal Enfeksiyonların Dağılımı



Neofytos D, et al. Clin Inf Dis 2009;48:265

Kandidemide erken tedavinin önemi

Murrell et al, AAC. 2005 49(9): 3640-5

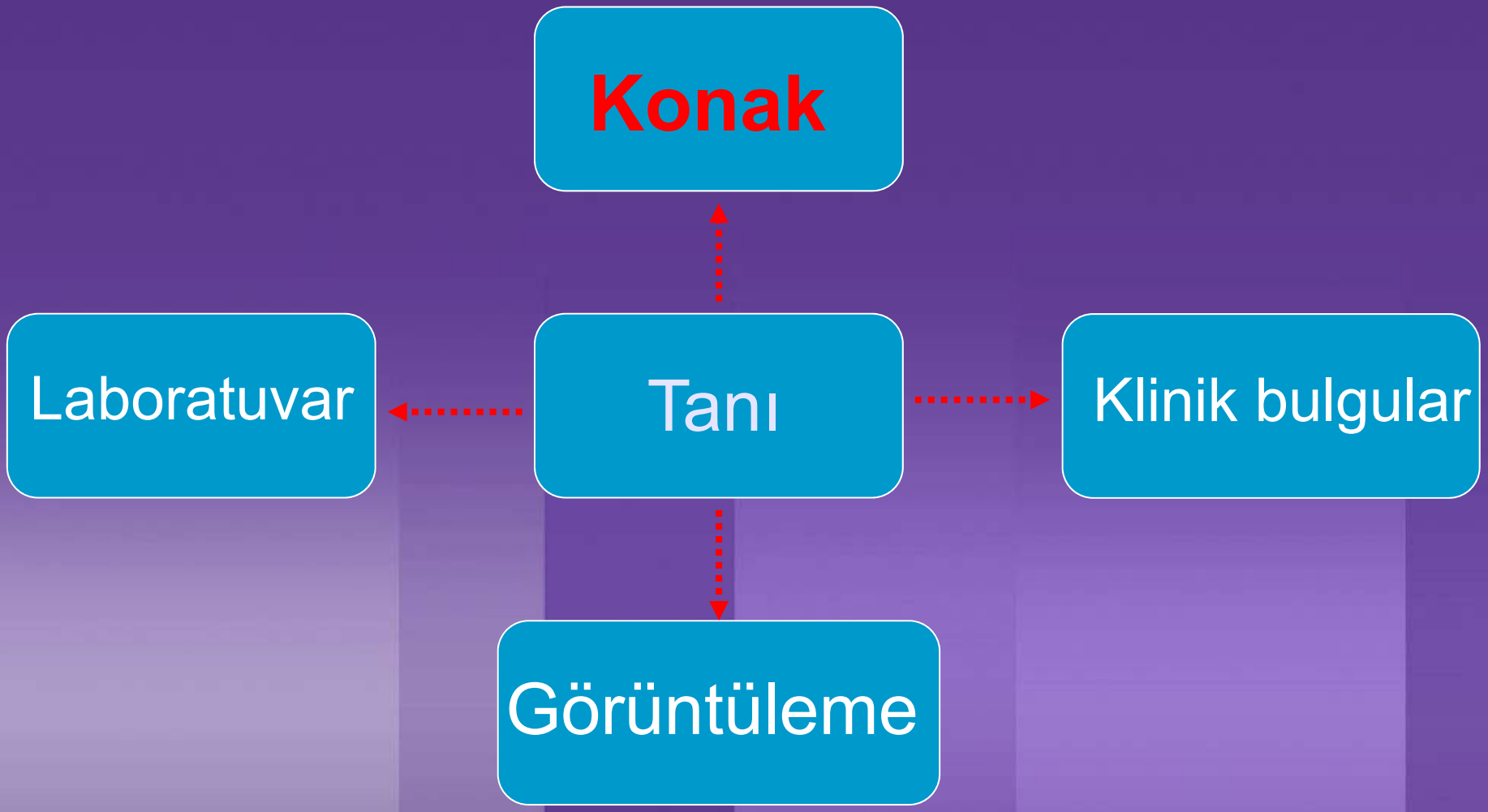


Multidisipliner Yaklaşım

- Kanıt arama
  - Radyoloji
    - YÇBT
  - Serum
    - Galaktomannan
    - Beta glukan
    - PCR
  - Bronkoskopi

- HEMATOLOJİ
- İNFEKSİYON HASTALIKLARI
- RADYOLOJİ
- MİKROBİYOLOJİ
- GÖĞÜS HASTALIKLARI

İnvazif fungal hastalıkların tanı süreci



İnvazif aspergillozun BT ile takibi

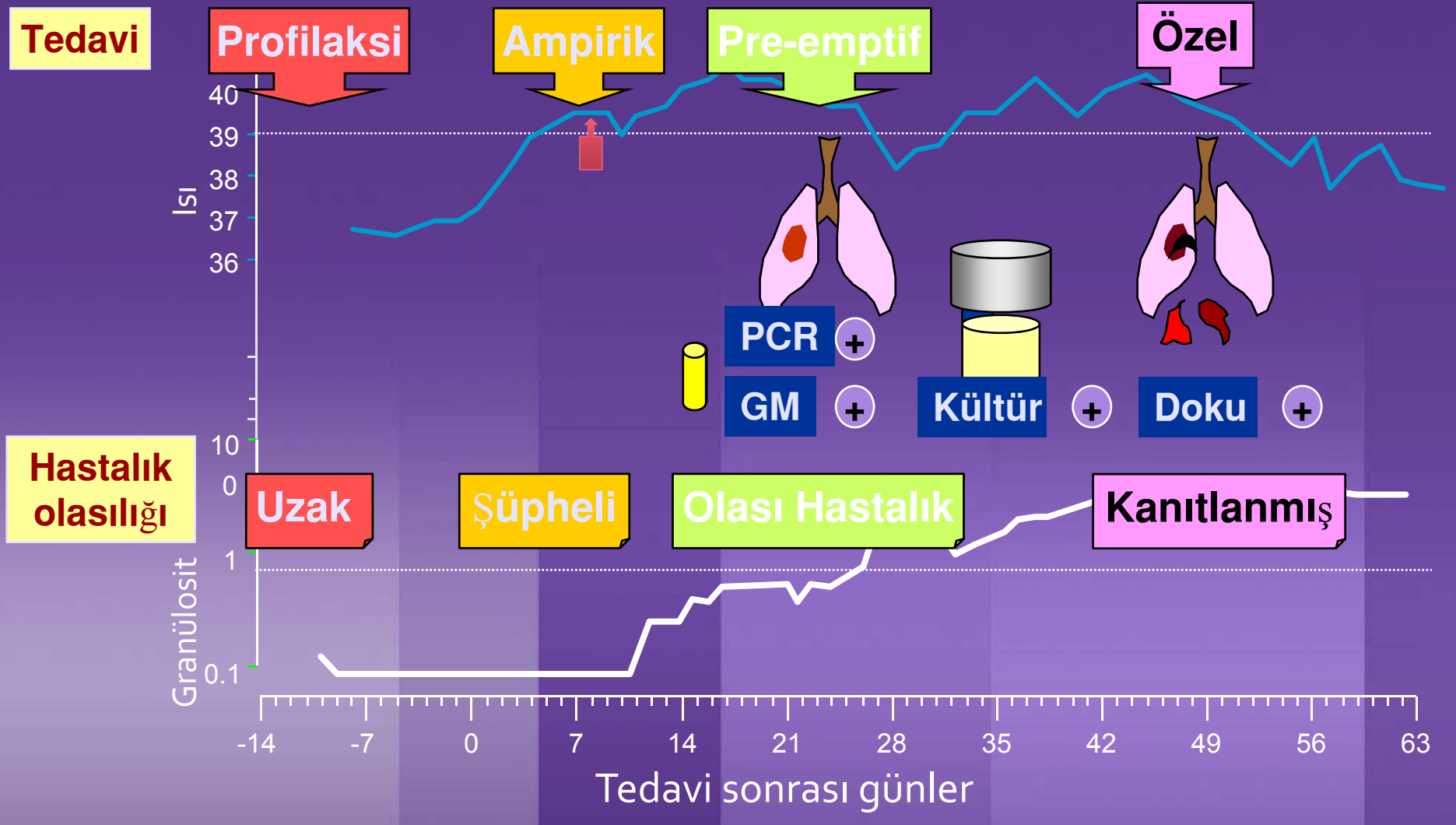
Çevresel halo | **Konsolidasyon** | **Hava-hilal bulgusu**

d0 - d5 | **d5 - d10** | **d10 - d20**

Nötropeni | **PMN >> 500**

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

TEDAVİ YAKLAŞIMLARI

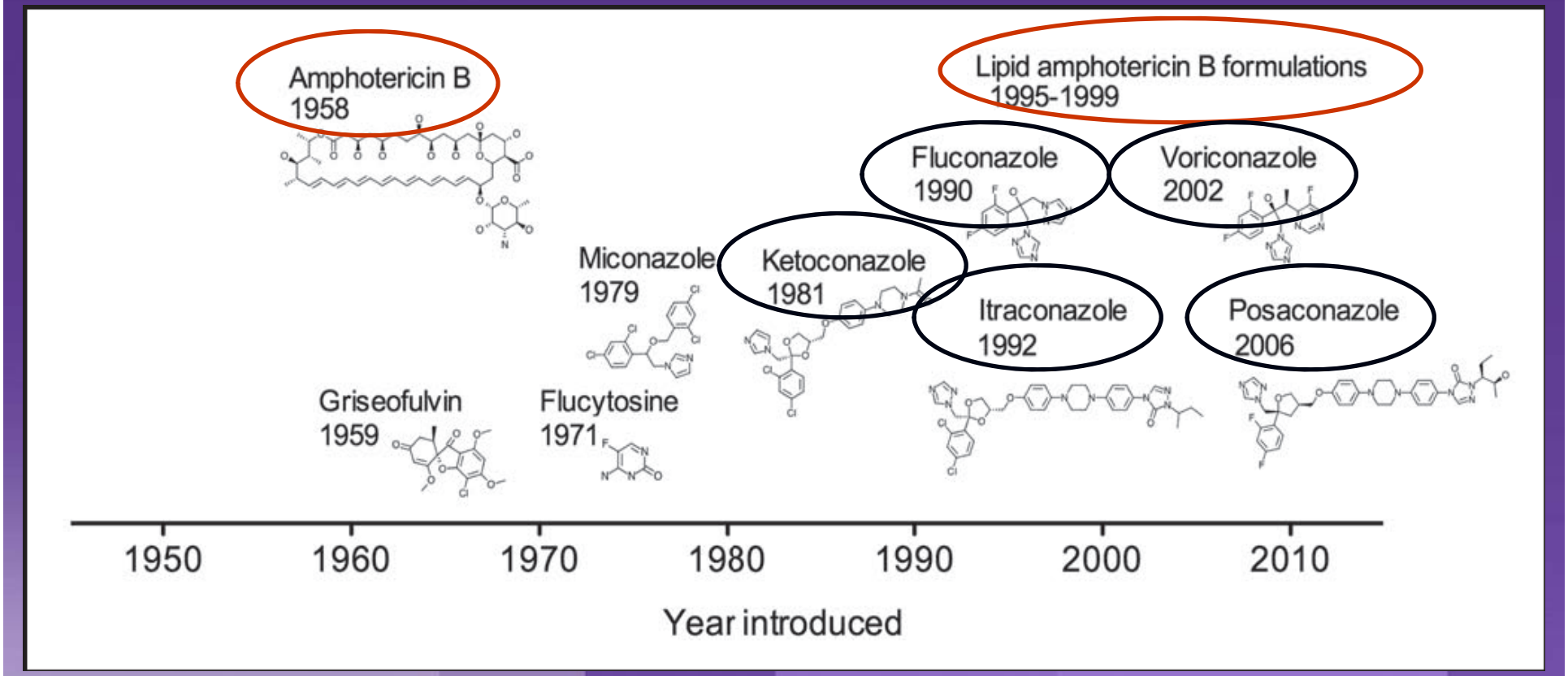


Ampirik - Preemptif

- YÇBT
- Galaktomannan

- Her zaman olası değil
- Pratikte hasta, hastane, hekim, zaman farklı kararlar

Antifungaller



Polyenler

Azoller

Ekinokandinler: Caspofungin, Micafungin
Anidulafungin

TABLE 1. **Comparative Pharmacokinetic and Pharmacodynamic Properties of Systemic Antifungal Agents**

Drug	Typical adult dosing	Oral bioavail-ability	C_{max} (μg/mL)	AUC (mg × h/L)	Protein (%)	CSF (%)	Vitreous (%)	Urine (%)	Metabo-lism	Elimina-tion	$T_{1/2}$ (h)
LAMB	3-5 mg/kg/d	<5	83	555	>95.0	<5	0-38[b,c]	5	Minimal urine; feces	Minor	100-153
FLU	6-12 mg/kg/d	>90	6-20	400-800	10.0	>60	28-75[b,c]	90	Minor hepatic	Renal	31
ITRA[d]	200 mg twice daily	50	0.5-2.3	29.2	99.8	<10	10[b]	1-10	Hepatic	Hepatic	24
VOR	6 mg/kg every 12 h for 2 doses, then 4 mg/kg every 12 h	>90	3.0-4.6	20.3	58.0	60	38[b,c]	<2	Hepatic	Renal	6
POS	600-800 mg/d in	ND	1.5-2.2	8.9	99.0	ND	26[b,c]	<2	Modest	Feces	25
CAS	70-mg loading dose, then 50 mg/d	<5	8-10	119	97.0	<5	0[b]	<2	Hepatic	Urine	30

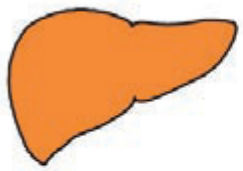
Diğer İlaçlarla Etkileşim Riski

TABLE 2. **Cytochrome P450 (CYP) Inhibition Profile of Triazole Antifungal Agents**

Mechanism	Flu-conazole	Itra-conazole	Posa-conazole	Vori-conazole
Inhibitor				
CYP2C19	+	–	–	+++
CYP2C9	++	+	–	++
CYP3A4	++	+++	+++	++
Substrate				
CYP2C19	–	–	–	+++
CYP2C9	–	–	–	+
CYP3A4	+	+++	–	+

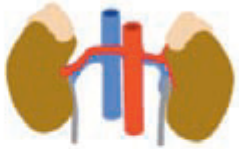
Advers Olaylar

Hepatic



All azoles
Amphotericin B
5-FC
Echinocandins

Renal toxicity



Amphotericin B
Cyclodextrins possibly toxic (IV voriconazole)

CNS

Voriconazole

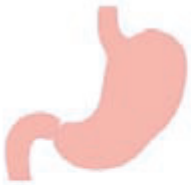
Photopsia

Voriconazole

Cutaneous

Rash (all antifungal agents)
Photosensitivity/malignancy? (voriconazole)

GI



Itraconazole
Posaconazole
5-FC

Cardiac

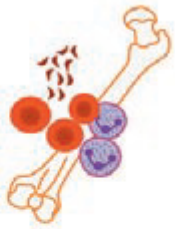
Cardiomyopathy (itraconazole)

QTc prolongation (all azoles, especially with drug interactions)

Infusion reactions

Amphotericin B
Echinocandins

Bone marrow suppression



5-FC

Amphotericin B (anemia associated with decreased epoetin production)

UPDATE ECIL- 3 2009

Antifungal prophylaxis in allogeneic SCT

Proposed changes only

Neutropenia w/o GvHD	
Fluconazole* 400 mg/d	AI
Posaconazole	No data
Voriconazole 200 mg bid	Provisional AI
GvHD > grade I	
Fluconazole 400 mg/d	CI
Posaconazole 200 mg tid	AI
Voriconazole 200 mg bid	Provisional AI

* combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

1st European Conference on Infection in Leukemia

UPDATE ECIL-3 2009: Summary slide

Primary antifungal prophylaxis in leukemia patients

- Induction chemotherapy of acute leukemia
  - Fluconazole 50-400 mg qd iv/oral: CI[2,5]
  - Itraconazole oral solution 2.5 mg/kg bid: CI[1,2,3]
  - Posaconazole 200 mg tid oral: AI[2,3]
  - Candins iv: insufficient data
  - Polyene[4] iv: CI
  - Aerosolized liposomal amphotericin B in combination with oral fluconazole: BI

1. may be limited by drug interactions and/or patient tolerability
2. azoles should not be used empirically in case of prior azole prophylaxis
3. it is recommended to monitor serum drug concentrations
4. includes low doses of conventional amphotericin B and lipid formulations.
5. combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI

1st European Conference on Infection in Leukemia

UPDATE ECIL- 3 2009

Secondary antifungal prophylaxis

- Condition:
  - Previously documented and fully resolved IFI plus
  - A new episode of
    - prolonged neutropenia (usually chemotherapy-induced)
    - severe immunosuppression (usually transplantation)
- Recommandation: AII
  - Cordonnier C, et al. Bone Marrow Transplant. 2004;33(9):943-8 and VOSIFI study presented at ASH 2008, San Francisco
  - Vehreschild JJ, et al. Int J Antimicrob Agents. 2009; 34(5):446-50.
  - Cornely O, et al. J Antimicrob Chemother. 2008 ;61(4):939-46.
  - Stute N, et al. Bone Marrow Transplant. 2004; 33 Suppl 1: S735
- No drug-specific recommendations possible, but choice should be based on the causative fungal pathogen of the previous IFI and the response to antifungal agents during that episode

1st European Conference on Infection in Leukemia

2009 UPDATE - Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

« Generally recommended. Moderate evidence »

Unchanged grading (no change in evidence)

UPDATE ECIL-3 2009

2009 UPDATE : Antifungal Drugs for Empirical Therapy

Antifungal agent	Daily dose	CDC Grading		
		Level of Recommendation	Evidence for	
			Efficacy	Safety
Liposomal AmB	3 mg/kg	A *	I	I
Caspofungin	50 mg	A *1	I	I
ABCD	4 mg/kg	B 2	I	I
ABLC	5 mg/kg	B 2	I	I
Itraconazole	200 mg iv	B 1,4	I	I
Voriconazole	2x 3 mg/kg iv	B 1,3,4	I	I
NEW: Micafungin	100 mg	B	II	II
AmB deoxycholate	0.5-1 mg/kg	B 2 / D 5	I	I
Fluconazole	**400 mg iv**	**C 1,4,6**	**I**	**I**

* A double-blind, randomized trial comparing caspofungin 50 mg/m² (n=56) with liposomal ampho B 3 mg/kg/d (n=25) (published in abstract form) suggests a provisional grading BII for children ; the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for 2011 update of ECIL guidelines

1 No activity against mucorales

2 Infusion-related toxicity (fever, chills, hypoxia)

3 Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis, effective therapy for candidiasis, and efficacious for prevention of breakthrough IFI.

4 Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.

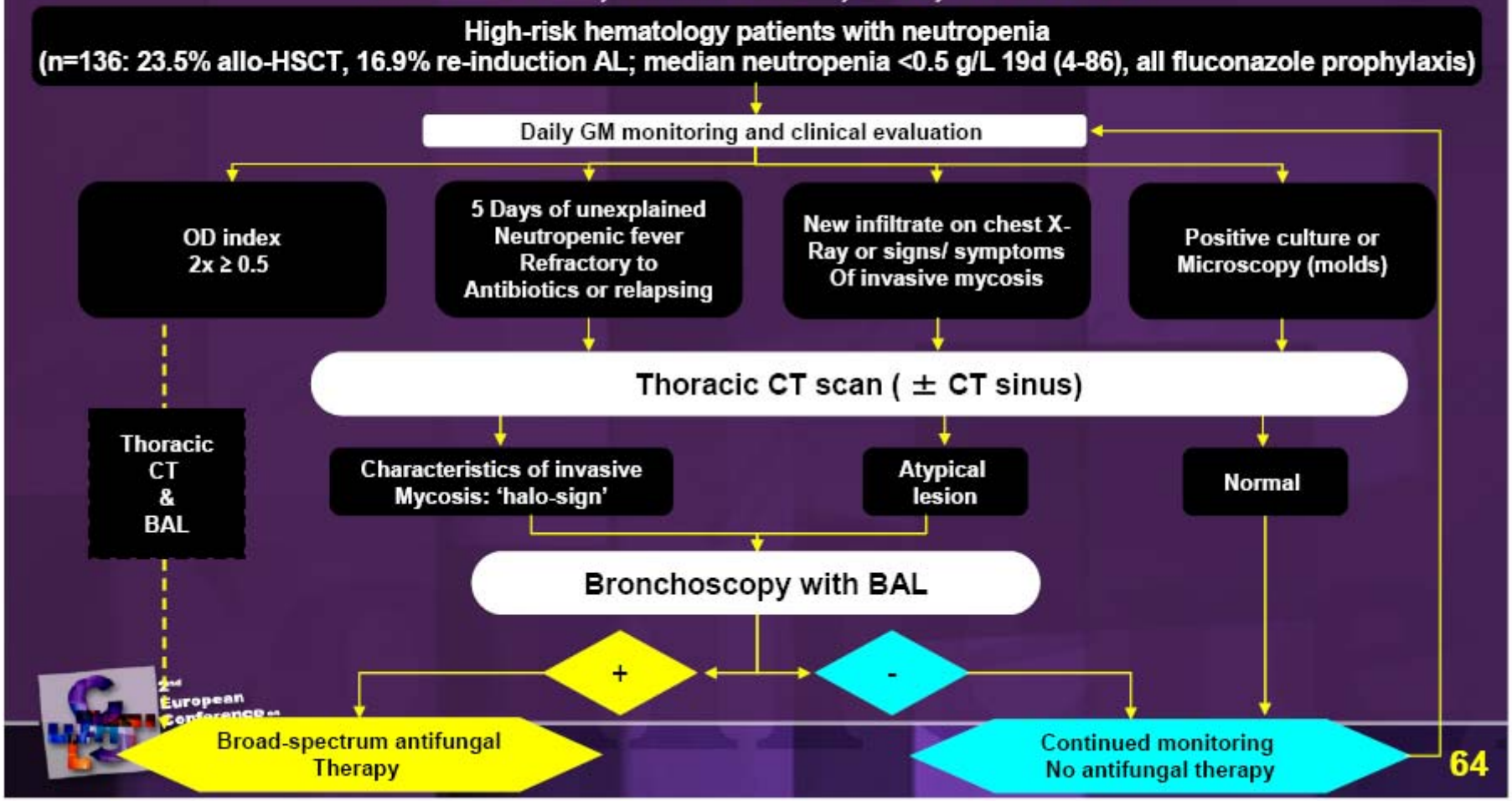
5 B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosprin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).

6 No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

UPDATE ECIL-3 2009

Galactomannan and CT-Based Pre-Emptive Antifungal Therapy: Prospective Feasibility Study

Maertens et al., Clin Infect Dis, 2005; 41: 1242-50



UPDATE ECIL-3 2009

Galactomannan and CT-Based Pre-Emptive Antifungal Therapy: Prospective Feasibility Study

Maertens et al., Clin Infect Dis, 2005; 41: 1242-50

4'170 galactomannan measurements: median 28 (range 5-96)/patient

↓

117 FEVER, 58 (49.6%) qualified for empirical antifungal therapy [30 (25.6%) for persistent fever and 28 (23.9%) for relapsing fever]: only 9 (7.7%) preemptive lipo-AmB
19 NO FEVER: 10 preemptive liposomal AmB for positive galactomannan

Preemptive liposomal AmB 5 mg/kg/d in 19 episodes:
- Galactomannan trigger in 16, persistent fever + CT-scan trigger in 3
- 7 proven inv. aspergillosis, IA (6 died, 2 due to IA), 12 probable IA (1 died, not IA)
- 3-month survival in IA 63.1% (76.9% if HEM remission, 30% if HEM refractory)

No antifungal therapy in 117 neutropenic episodes:
- 2 *C. glabrata* breakthrough fungemia, 1 disseminated zygomycosis, no IA
- 9 deaths (1 due to zygomycosis)

2nd European Conference on Infections in Leukemia

UPDATE ECIL-3 2009

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT): Multicenter, Open-Label Randomized Trial

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51

Prospective, 12 French centers, 2003-6 in adult, hematological cancer, myeloablative chemotherapy or auto-HSCT, expected neutropenia <0.5 G/L during >10 D, no previous IFI

↓

Stratified (center / chemotherapy / prophylaxis)
randomization strategy 1:1 applied from day 4 to day 14 of fever

Empirical Antifungal Rx

Fever-driven

Pre-Emptive Antifungal Rx

If pneumonia, septic shock, skin lesions, acute sinusitis/orbital signs, unexplained CNS signs, hepatosplenic abscesses, grade 3-4 mucositis, severe diarrhea, *Aspergillus* colonization, or ≥ 1x GM Ag ≥ 1.5 (2x/week)

AmB-deoxy (1mg/kg/d) if Cr-Cl > 60 or 40-59 ml/min and NO nephrotoxic agents
Liposomal AmB (3mg/kg/d) if Cr-Cl 40-59 + nephrotoxic agent or Cr-Cl <40 ml/min

PRIMARY ENDPOINT: SURVIVAL 14 D AFTER RECOVERY NEUTROPENIA (60 D if no recovery), expected 90%, NON-INFERIORITY IF D < 8% (228 pts needed in each arm)
SECONDARY ENDPOINT: OCCURRENCE OF PROVEN/PROBABLE IFI

UPDATE ECIL-3 2009

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT)

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51

Reason for starting antifungal therapy

Days fever onset to antifungal therapy

Days antifungal therapy

Table 3. Antifungal therapy in the intention-to-treat population (n = 293).

End point	Empirical treatment group	Preemptive treatment group	P^a
Antifungal treatment	92/150 (61.3)	56/143 (39.2)	<.001
Reason for starting antifungal treatment[b]			
Isolated fever between day 4 and day 14 after antibacterial treatment initiation	55 (59.8)	1 (1.8)	<.001[c]
Pneumonia	6 (6.5)	26 (46.4)	
Severe mucositis	8 (8.7)	10 (17.9)	
Isolated fever beyond day 14	11 (12.0)	7 (12.5)	
Septic shock	5 (5.4)	3 (5.4)	
Positive result of galactomannan antigen test	2 (2.2)	3 (5.4)	
Skin lesion	2 (2.2)	2 (3.6)	
Sinusitis or periorbital inflammation	0 (0.0)	3 (5.4)	
Neurological symptoms	2 (2.2)	0 (0.0)	
Diarrhea	1 (1.1)	1 (1.8)	
Duration of fever before antifungal treatment,[b] median days (IQR)	7 (5–11)	13 (6–17)	<.01
Duration of fever after antifungal treatment,[b] median days (IQR)	9 (4–15)	7 (5–13)	NS
Duration of antifungal treatment, mean days ± SD			
Any antifungal agent	7.0 ± 8.5	4.5 ± 7.3	<.01
High-cost antifungal agents (liposomal AmB, caspofungin, or voriconazole)	3.7 ± 7.6	2.6 ± 5.8	NS
Low-cost antifungal agents (AmB deoxycholate)	3.5 ± 5.2	2.0 ± 4.6	<.01
Cost of antifungal drugs, 2005 €			
Mean ± SD	2252 ± 4050	1475 ± 3329	<.001
Range	0–20,726	0–18,500	
Estimated cost of antifungal drugs if liposomal AmB had been used instead of AmB deoxycholate, 2005 €			<.001
Mean ± SD	4261 ± 4760	2509 ± 4099	

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UPDATE ECIL-3 2009

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT)

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51

Primary Endpoint: Survival

Secondary Endpoint: Invasive fungal infection (IFI)

Total days fever

Table 2. Efficacy end points in the intention-to-treat population (n = 293).

Efficacy end point	Empirical treatment arm (n = 150)	Preemptive treatment arm (n = 143)	Difference (95% CI)	P^a
Primary				
Alive at study completion	146 (97.3)	136 (95.1)	−2.2 (−5.9 to 1.4)	.31
Secondary				
IFI	4 (2.7)	13 (9.1)	−6.4 (−10.9 to −1.9)	<.02
Baseline IFI due to				
Aspergillus species	2	6	…	
Candida species	0	3	…	
Breakthrough IFI due to				
Aspergillus species	2	2	…	
Candida species	0	2	…	
IFI-related mortality	0 (0)	3 (2.1)	−2.1 (−4.1 to 0.0)	.11
Duration of temperature ≥38°C,[b] days				
Median (IQR)	13 (5–21)	12 (5–20)	…	NS
Range	1–42	1–59	…	

NOTE. Data are no. (%) of patients, unless otherwise indicated. IFI, invasive fungal infection; IQR, interquartile range; NS, not significant.

[a] By Cochran-Mantel-Haenszel test for qualitative variables; by Wilcoxon sum-rank test for skewed quantitative variables.

[b] Excludes 14 patients without fever (8 in the empirical treatment group and 6 in the preemptive treatment group).

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Comments

A pre-emptive antifungal strategy is "FEASIBLE"

- Clinical + GM/CT-scan based pre-emptive: overall survival as with empirical
- Decreased use of antifungal therapy vs. empirical
- Risk of increased occurrence of IFI (*Aspergillus, Candida*) vs. empirical therapy, especially in patients with neutropenia during more than 15 days: prognostic impact of IFI ?
- Potential for early therapy of IFI in absence of fever with pre-emptive approach (missed by fever-driven empirical approach)
- No grading of evidence/recommendation for pre-emptive due to the lack of defined standard criteria and variability of results among studies

Antifungal Therapy in Leukemia Patients

UPDATE ECIL 4, 6 September 2011

Raoul Herbrecht, Ursula Flückiger, Bertrand Gachot,

Patricia Ribaud, Anne Thiebaut, Catherine Cordonnier

Recommendations Aspergillosis

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UPDATE ECIL 3, 2009

Invasive pulmonary aspergillosis :1st line

Agent	Grade	Comments
Voriconazole	A I	2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)
Ambisome	B I	dose 3 – 5 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C II	
Itraconazole	C III	start with iv
ABCD	D I	
Amphotericin B deoxycholate	D I	
Combination	D III	

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

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UPDATE ECIL 3, 2009

Invasive aspergillosis: salvage

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

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Invasive pulmonary aspergillosis: antifungal combinations

- First line
  - Not recommended — DIII
- Salvage
  - Caspofungin + lipid ampho B — C II
  - Caspofungin + voriconazole — C II
  - Ampho B (any formulation) + azole: — no data

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Aspergillosis: unsolved questions

- Duration of therapy
  - No fixed duration
- Drug monitoring, especially for azoles, may be indicated in case of failure or of adverse events
- In vitro testing
  - Filamentous fungi are not routinely tested for susceptibility
  - No correlation between susceptibility testing and outcome
  - *Identification to the species level is recommended : C III*

Recommendations Candidiasis

UPDATE ECIL 3, 2009

Candidemia in hematologic patients before species identification

	Overall population	Hematological pts
Micafungin	A I	B II
Anidulafungin	A I	B II
Caspofungin	A I	B II
Ambisome	A I	B II
Other lipid-AmB	A II	B II
AmB deoxycholate		A I * C III *
Fluconazole	A I **	C III
Voriconazole	A I ***	B II

** DIII if concomitant nephrotoxic drug and EIII if renal impairment*
*** Not in severely ill patients or in patients with previous azole prophylaxis*
*** Not in patients with previous azole prophylaxis*

3rd European Conference on Infections in Leukemia

Duration of antifungal therapy in candidemia : recommendations

Non-neutropenic adults: at least 14 days after the last +ve blood culture and resolution of signs and symptoms : **B III**

Neutropenic patients: at least 14 days after the last +ve blood culture and resolution of signs and symptoms and resolved neutropenia: **C III**

Importance of an active search for dissemination of infection in leukemic patients following neutrophil recovery (ocular fundus + abdominal imaging)

Şiddete Karşıyız

- Mantarın şiddeti
- HEKİM
- Hastanın Şiddeti