Hematolojik Malinite Hastalarında İnvazif Fungal Enfeksiyonlar

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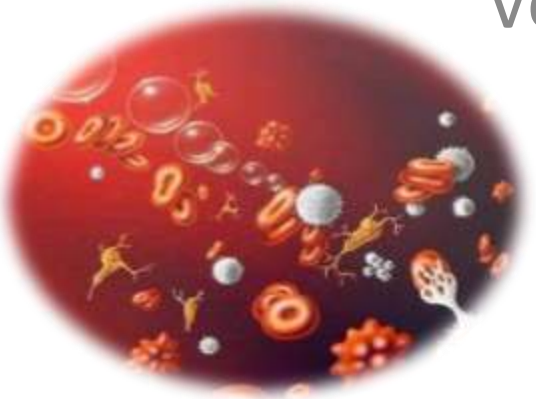
Çukurova Ünv. Tıp Fak. Enfeksiyon Hast. Ve Klin. Mikrobiol AD, Adana

6 Aralık 2019, Gaziantep

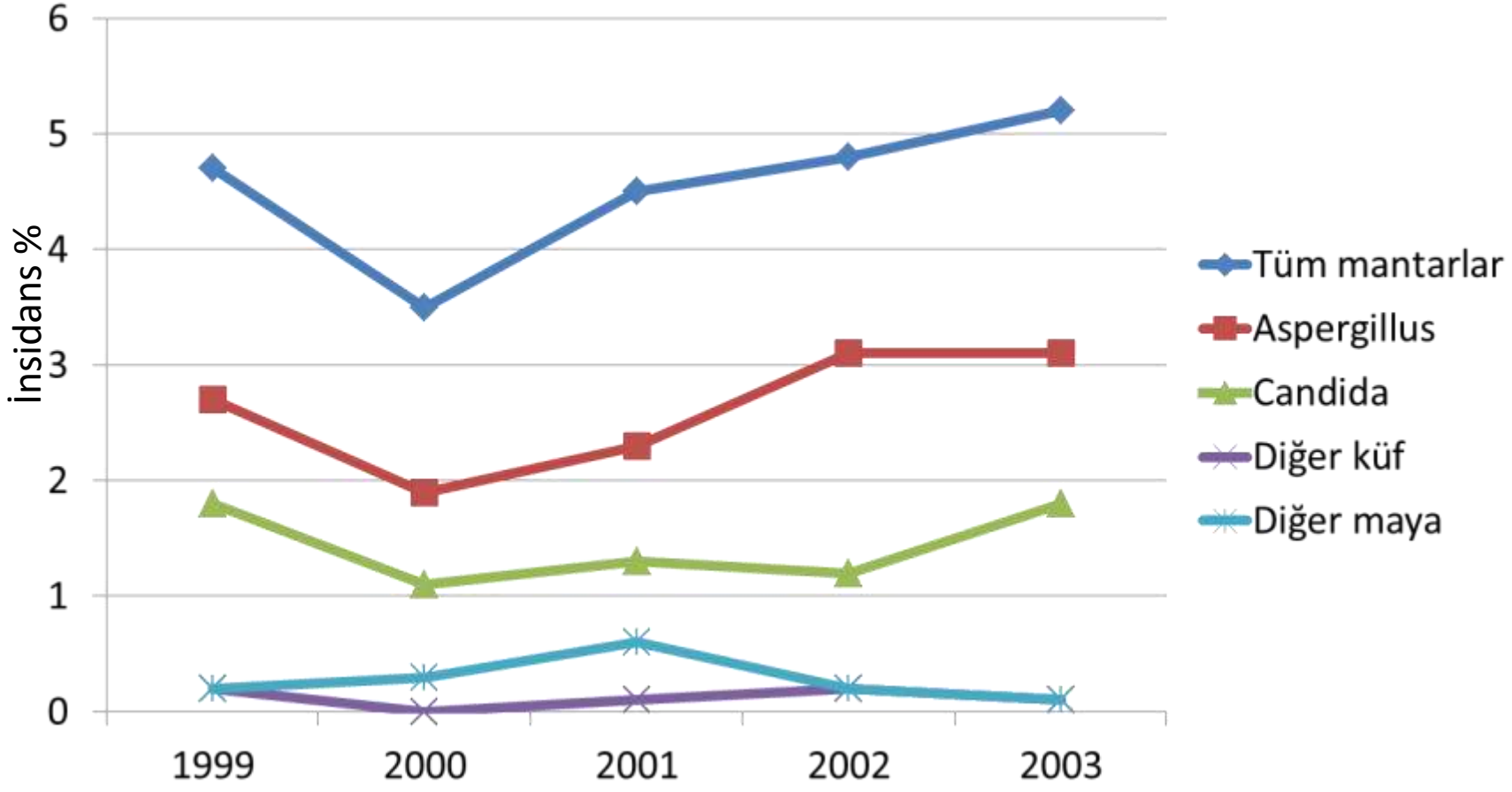


Hematolojik Malinite Ve İFE Olan Hastalarda Sorunlar

- Değişen epidemiyolojiyi
- İFE nonspesifik görünümleri
- Yetersiz tanı olanakları
- AF profilaksi- işe yarıyor mu?
- AF tedavi alırken gelişen *“Breakthrough”* enfeksiyonlar
- Antifungallere direnç
- İlaç etkileşimleri

Hematolojik Maligniteli Hastalarda İFİ Epidemiyolojisi

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



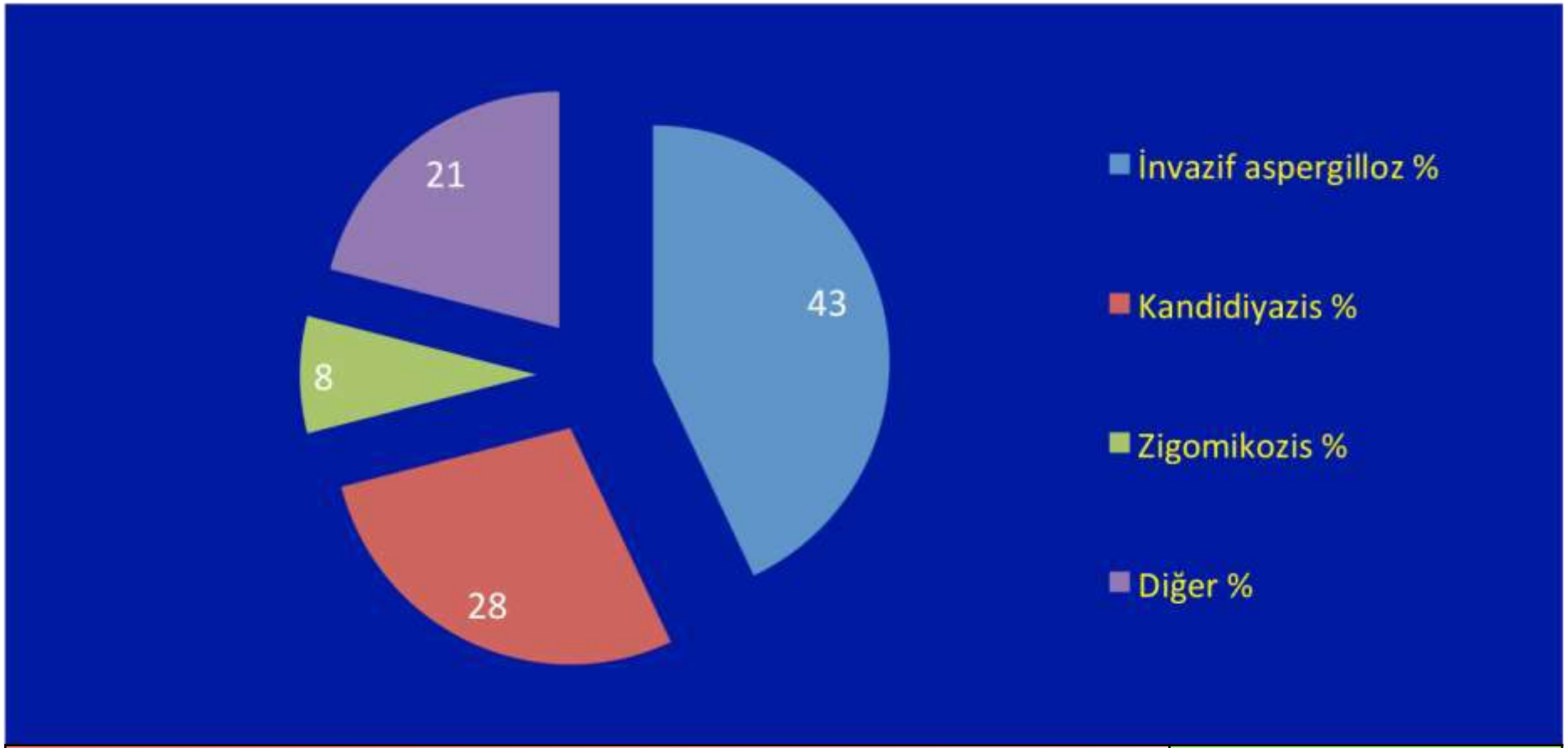
Hematolojik Kanserlerde İFE

	Risk (%)
Akut miyeloid lösemi	10-25
Miyelodisplastik sendrom	4.8-12
Akut lenfoblastik lösemi	6.5-23
Kronik lenfoproliferatif hastalıklar	0.5-10.8
Nonhodgkin lenfoma	2.6
Hodgkin lenfoma	0.3-1.2
Multiple miyelom	0.4-14
Kronik lenfositik lösemi	0.5-7.8
KİT	
Otolog kök hücre nakli	3-8
Allojenik kök hücre nakli	7-15

TRANSNET – ABD, 23 merkez, KİT Hastalarında İFİ (2001-2006)

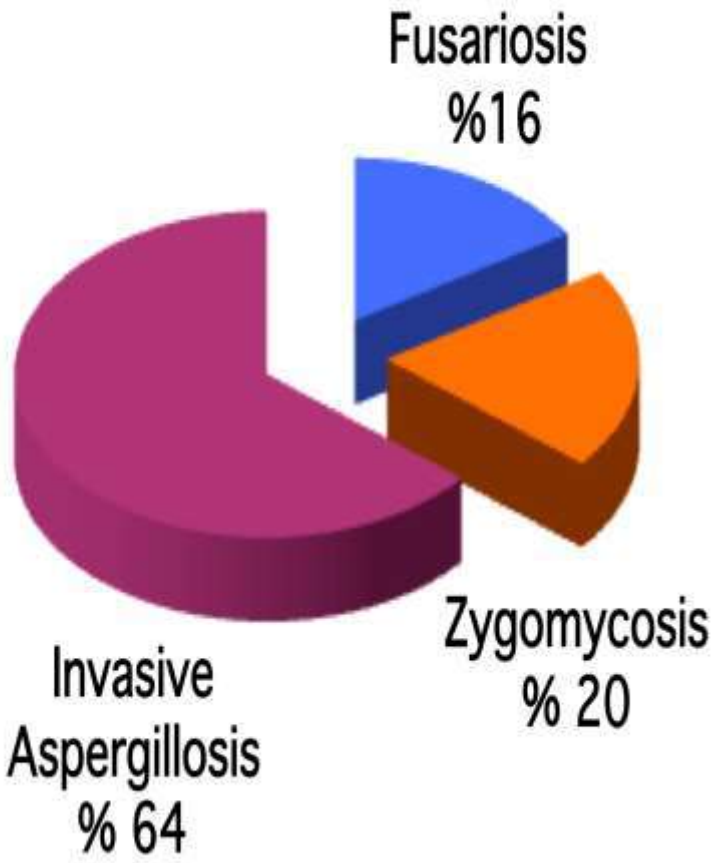
875 HSCT alıcısında gelişen 983 İFİ dağılımı

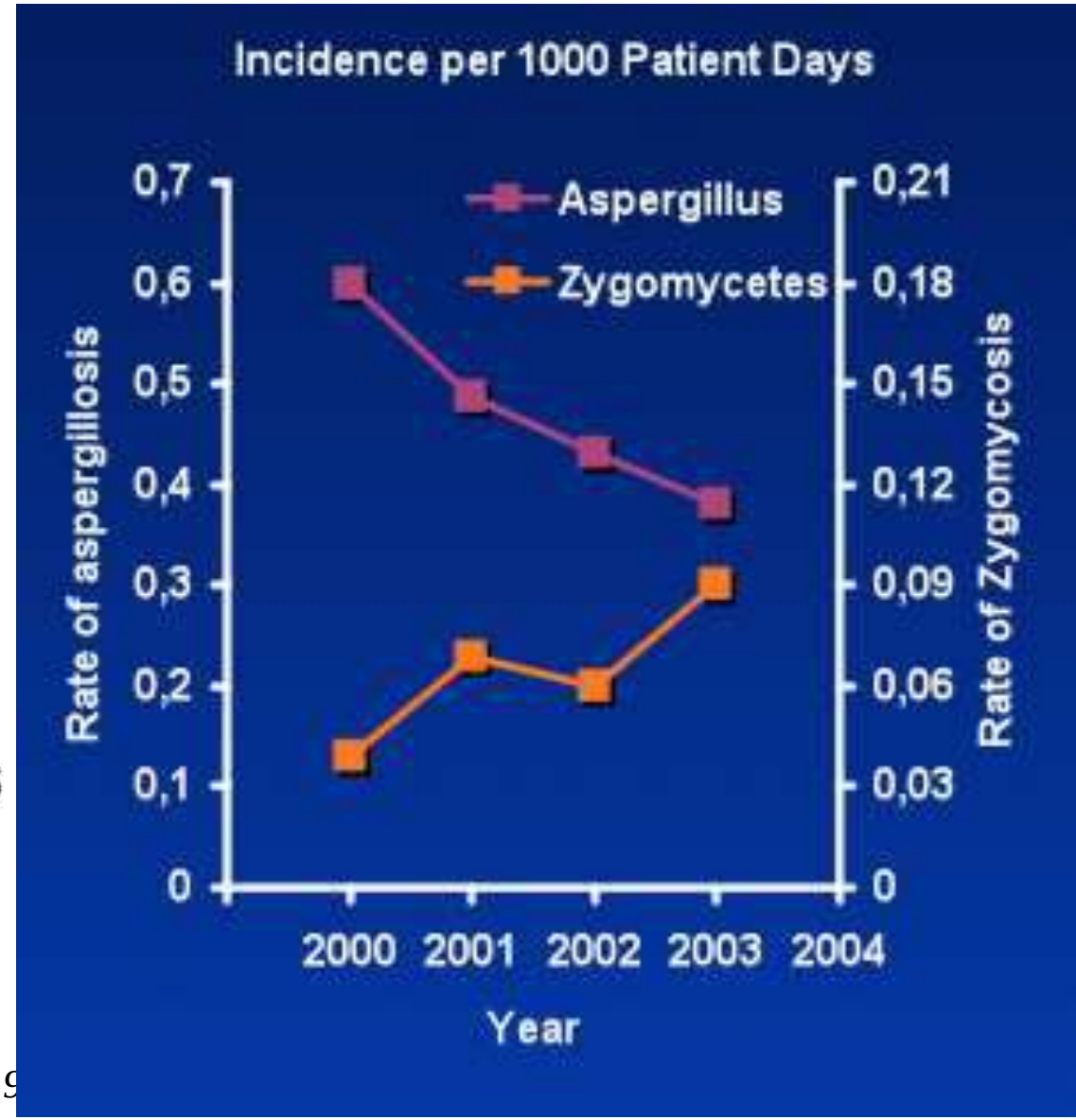
.Kontoyiannis et al CID 2010; 50:1091



Allojenik HSCT (/ 100 transplant)			Otolog HSCT (/ 100 transplant)
Doku uyumlu-akraba dışı	Doku uyumsuz-akraba	Doku uyumlu-akraba	
7	8.1	5.9	1.2

İnvazif Küflerde Spektrumda Değişme





Kontoyiannis DP, et al. J Infect Dis. 2005;19

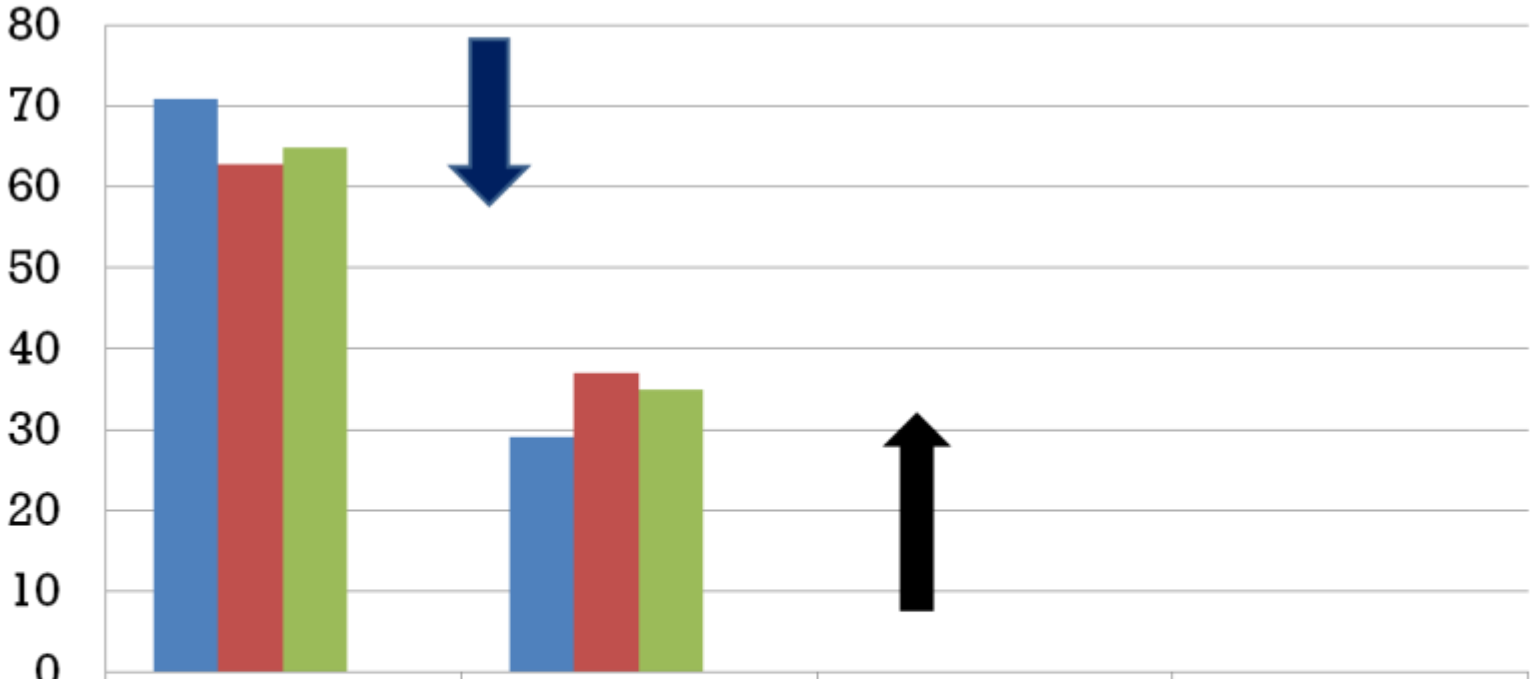
- KİT hastalarında non-*Aspergillus* küfleri azdır.
- En sık *Fusarium* ve *Scedosporium etkendir.*
- Mukormikozis de artmaktadır.
  - Vorikonazol profilaksisi ve *"breakthrough"* mukormikoz
  - Posakonazol profilaksisi sonrası da oluştu.*,**,***
    - Sadece bazı *Mucorales türleri*
  - Vorikonazol öncesi de artış var.
    - Çok faktörlü – immunsupresyonun değişimi, hastaların sağ kalımı

Kontoyiannis DP et al. Clin Infect Dis. 2010;50(8):1091–100.
Park BJ et al. Emerg Infect Dis. 2011;17(10):1855–64.
Nucci M et al Clin Infect Dis. 2005;41(4):521–6.
Lerolle N et al.Clin Microbiol Infect. 2014;20(11):952–9.
****KangSH et al. Infect Chemother. 2015;47(1):49–54.***
*****Lekakis LJ et al. Biol Blood Marrow Transplant. 2009;15(8):991–5.***

256 882 *Candida* spp

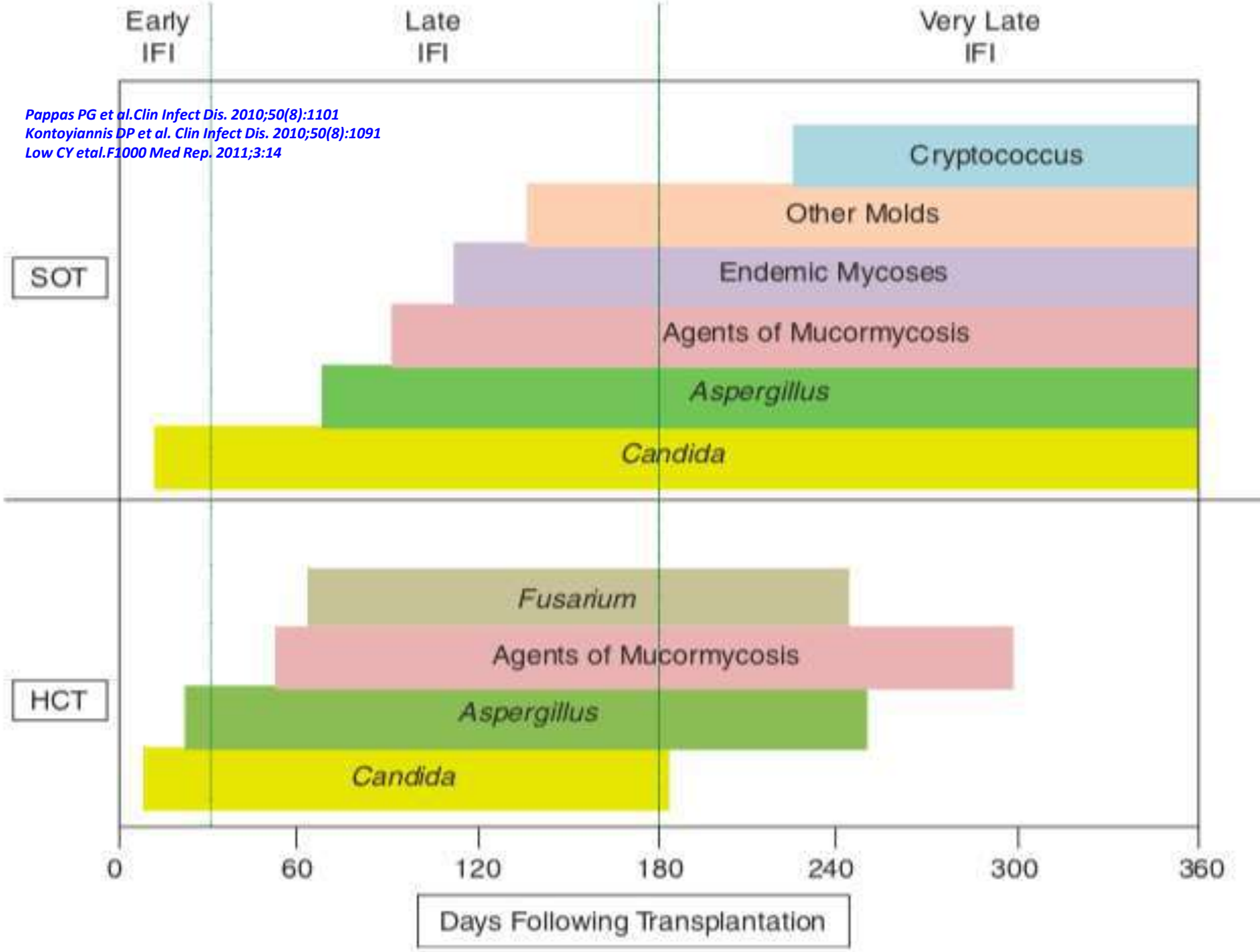
142 bölge, 41 ülke

ARTEMİS 1997-2007



	C.albicans	C.nonalbicans		
1997-2000	70,9	29,1		
2001-2004	62,9	37,1		
2005-2007	65	35		
Sütun1				

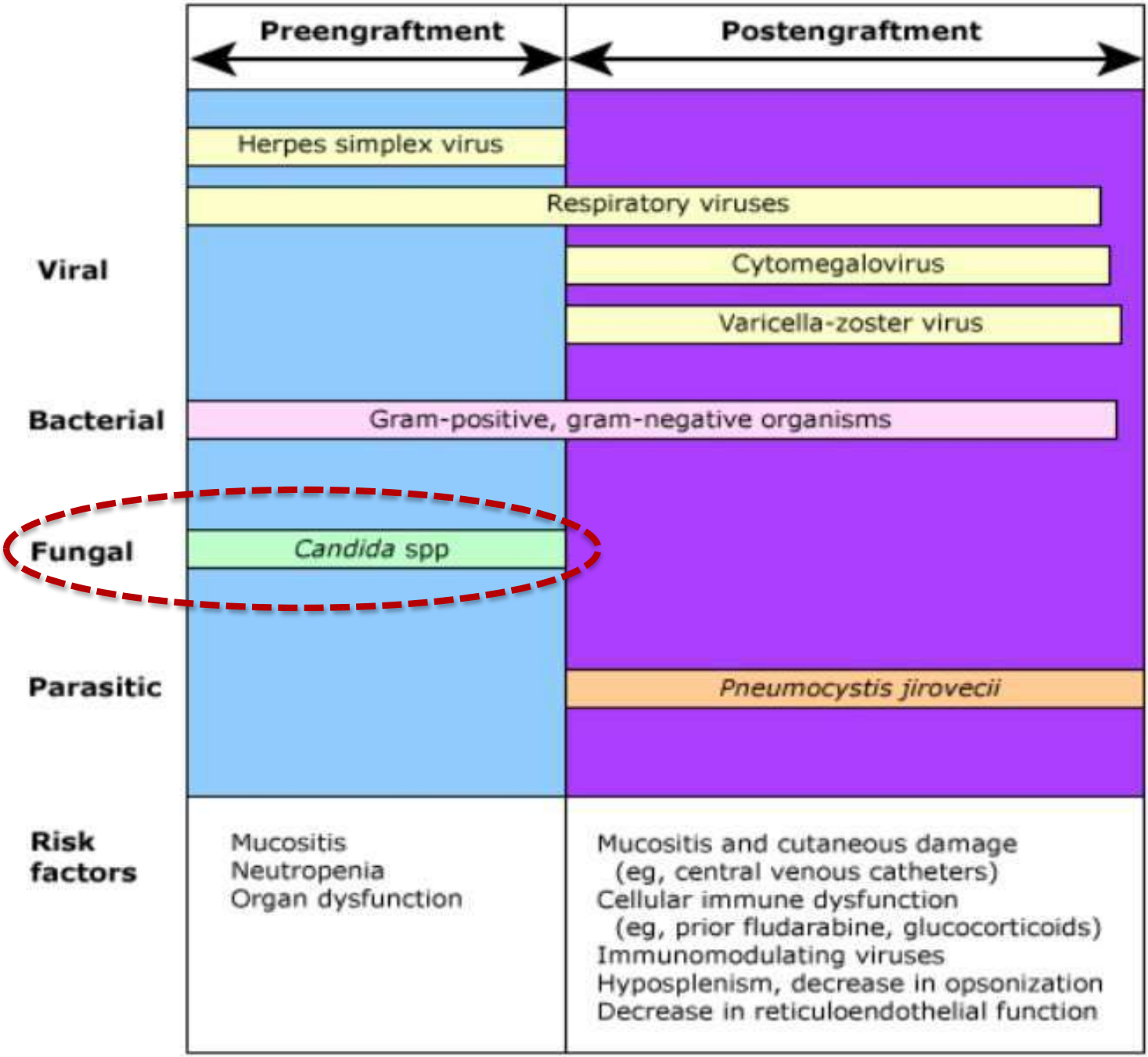
Pfaller MA et al. JCM 2010;48(4):1366


Early IFI
Late IFI
Very Late IFI
Pappas PG et al.Clin Infect Dis. 2010;50(8):1101
Kontoyiannis DP et al. Clin Infect Dis. 2010;50(8):1091
Low CY etal.F1000 Med Rep. 2011;3:14
SOT
Cryptococcus
Other Molds
Endemic Mycoses
Agents of Mucormycosis
Aspergillus
Candida
HCT
Fusarium
Agents of Mucormycosis
Aspergillus
Candida
0
60
120
180
240
300
360
Days Following Transplantation

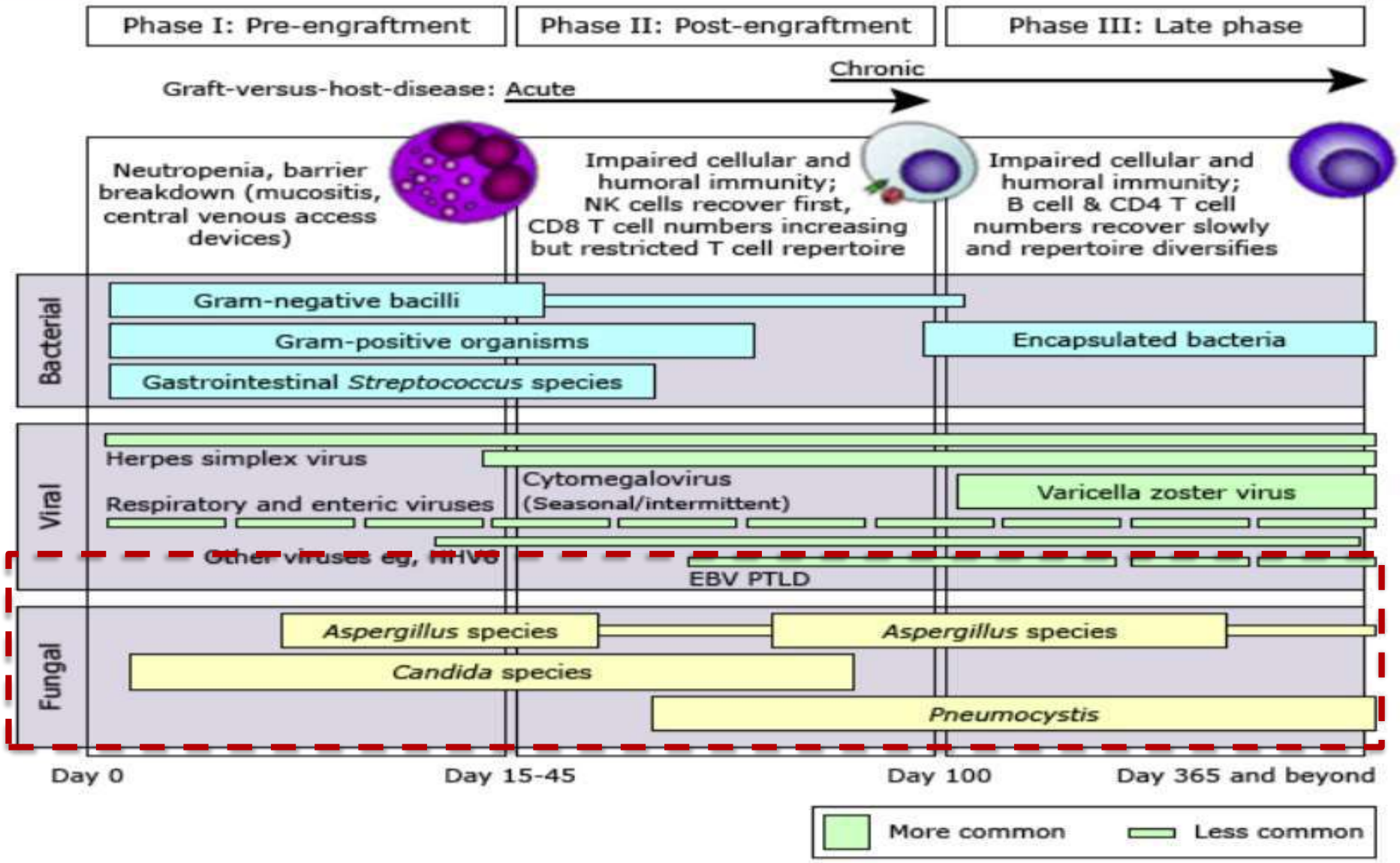
KİT İFE İçin Risk Faktörleri

Risk faktörleri	Özellikler
Transplant ilişkili	
Donor HLA benzerliği	Otolog < allojeneik (MRD<MMRD<URD)
Kök hücre kaynağı	Periferik kan<Kİ<kord kanı; T hücre kaybı/CD34 seçilmiş hücreler
Kondüsyon rejimi	NMA<MA – erken enfeksiyon NMA ≥ MA – geç enfeksiyon
PostTX ilişkili	
Nötropeni	Özellikle erken dönemde
Viral hastalık	CMV (en sık ilişkili) RSV, parainfluenza, +/- influenza
GVHD	Hem akut (özellikle grade III-IV) ve kronik GVHD ve tedavi ilişkili (örn KST, TNF-alfa blokerler)

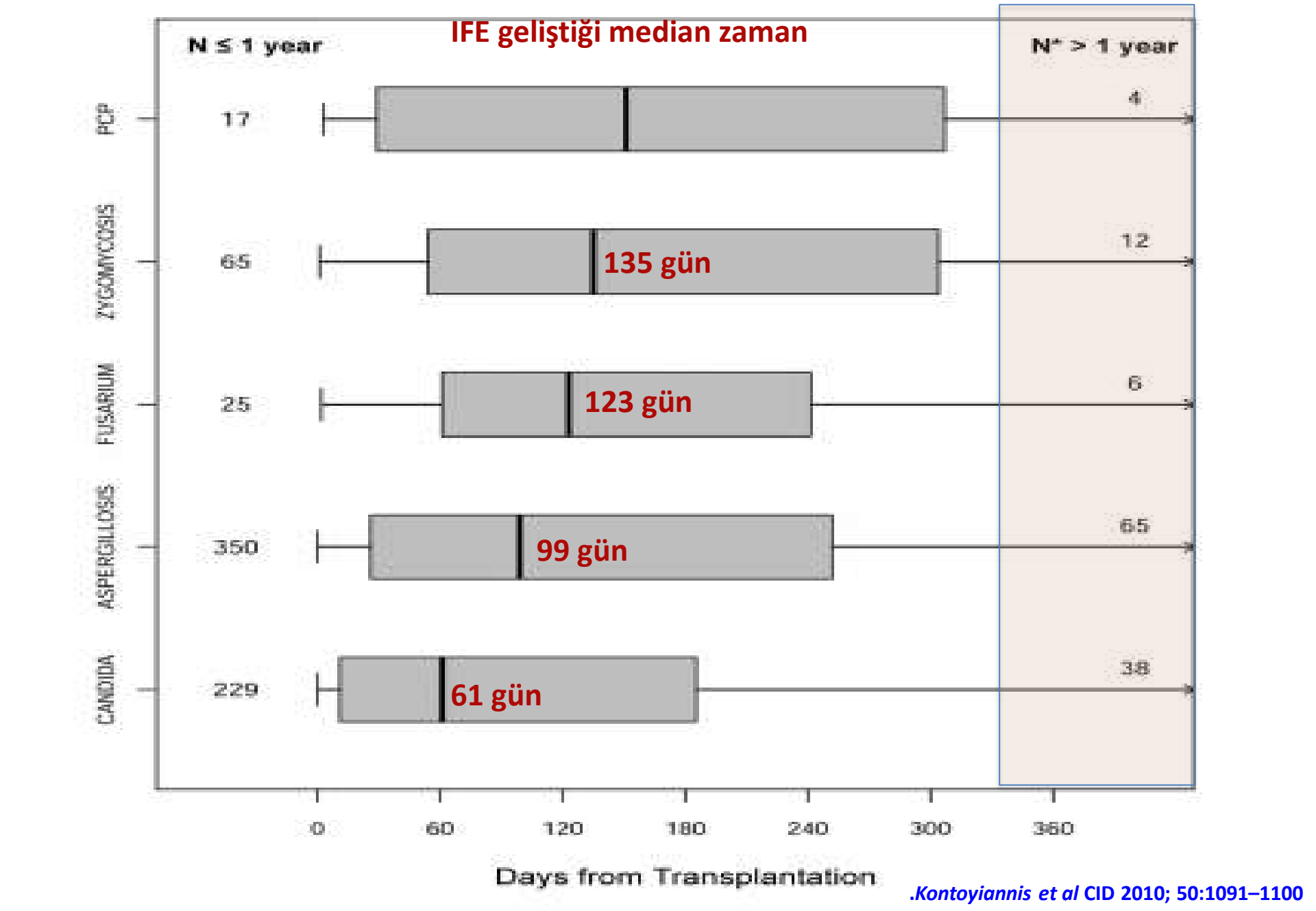
Typical timing of infections among autologous hematopoietic cell recipients receiving antimicrobial prophylaxis



Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients



EBV: Epstein-Barr virus; HHV6: human herpesvirus 6; PTLD: posttransplant lymphoproliferative disease



.*Kontoyiannis et al* CID 2010; 50:1091–1100

Figure 1. Distribution of time to invasive fungal infection (IFI) stratified by infection type (all IFI cases in surveillance cohort). N, number of IFIs in first year; N, number of IFIs occurring after 1 year; PCP, pneumocystosis.*

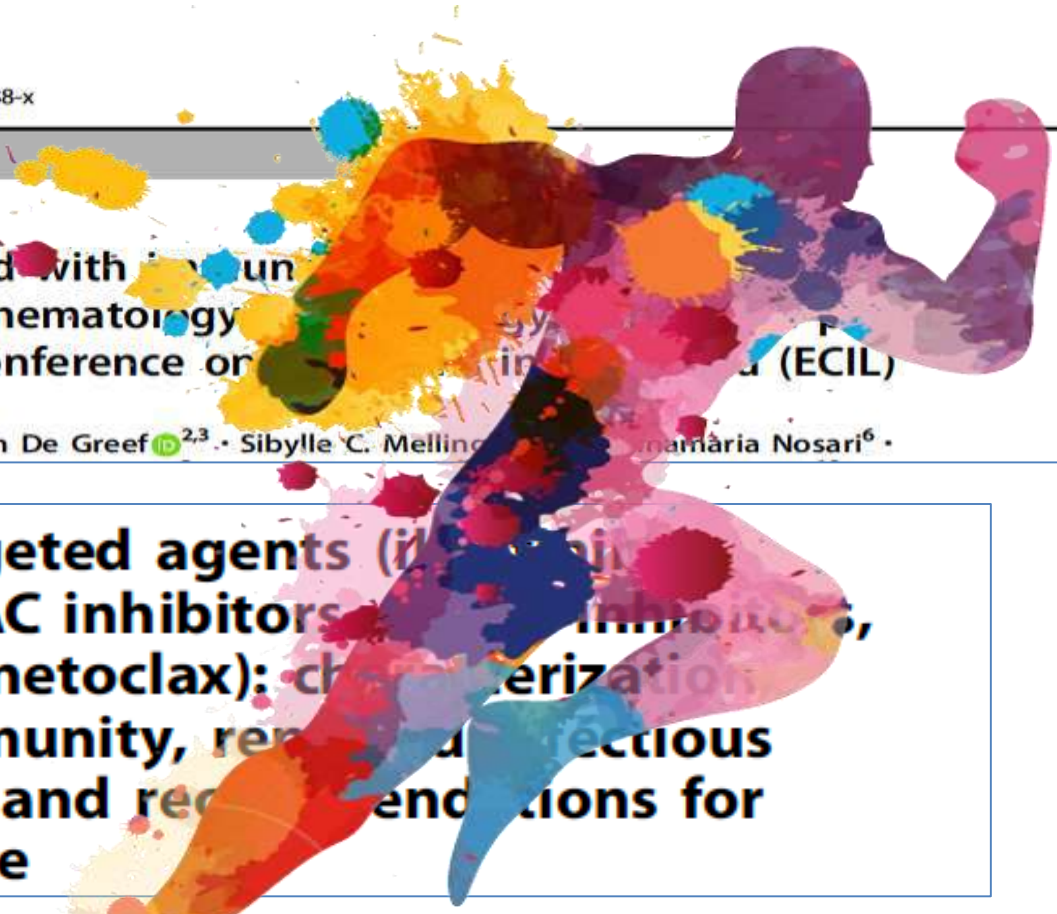
Leukemia
https://doi.org/10.1038/s41375-019-0388-x

REVIEW ARTICLE

Infectious medicine, virology

Infections associated with i un targeted agents in hematology by the European Conference on i d (ECIL)

Georg Maschmeyer[1] · Julien De Greef[2,3] · Sibylle C. Melling · amária Nosari[6] ·



Molecular targeted agents (i idelalisib, HDAC inhibitors , ruxolitinib, venetoclax): ch erization, impact on immunity, re ectious complications and re endations for clinical practice

Immunot apeutic agents (blinatumomab, brentux ab vedotin, immune checkpoint inhibitors): characterization, impact on immunity, reported infectious complications and recommendations for clinical practice

Yeni İmmunmodülatör Tedaviler Ve İFE

- **Anti B –cell ajan – ibrutinib(imbruvica) - KLL ve lenfoma**
  - **Aspergilloz, kriptokokoz, alışılmadık ve agresif İFE artış**
  - Steroid ile verilmesi de etkili
  - İlk indüksiyon tedavisinin zamanı İFE için en yüksek riskli dönem

Chamilos G et al.Clin. Infect. Dis. 66, 140–148 (2018).

- **Checkpoint inhibitörler** – ipilimumab, nivolumab, pembrelizumab- kansere immun yanıtı arttırır.
  - İFE arttırmaz.
  - Steroid+ anti- TNF (influximab) kullanılır. Bu kombinasyon İFE (İA) arttırır.

Pagano and Major. FutureSci.OA(2018)FSO307

Busca A & Pagano L (2018): Prophylaxis for aspergillosis in patients with haematological malignancies: pros and cons, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2018.1496329

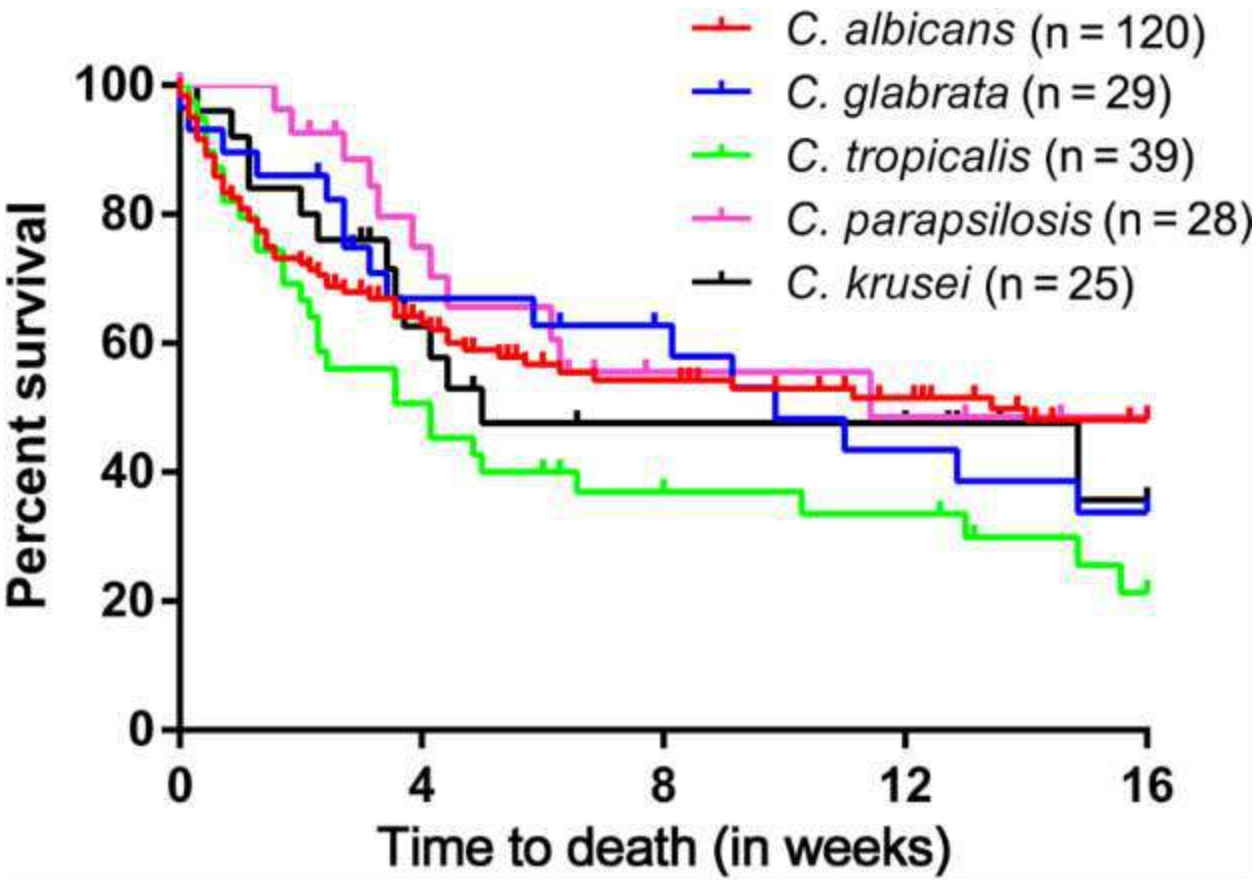
Table 1. Interactions of mold-active azoles (voriconazole and posaconazole) with coadministered chemotherapic agents and target therapies.

COADMINISTERED AGENT	INTERACTION MECHANISM	EFFECT	RECOMMENDATIONS AND ACTIONS
Vinca Alkaloids	Inhibition CYP3A4	Increased neurotoxicity	Avoid coadministration
Vincristine [87,88]			
Alkylating agents	Inhibition CYP3A4/2C9	↑ hepatotoxicity	Monitor
Cyclophosphamide (CTX) [87,88]		↓ activation to hydroxy-CTX	Avoid coadministration
Bruton's tyrosine kinase inhibitors	Inhibition CYP3A4/2C9	↑ Ibrutinib exposure	420 mg standard dose
Ibrutinib			280 mg if Fluco;
			140 mg if Posa/vori
PI3K inhibitors	Inhibition CYP3A4/Pgp	↑ AUC	Monitor for side effect
Idelalisib			
JAK2 inhibitors	Inhibition CYP3A4/2C9	↑ Ruxolitinib exposure	↓ dose 50%; monitor cytopenias
Ruxolitinib [89]			
TKI			
Imatinib [89,90]	Inhibition CYP3A4	↑ Imatinib exposure	Avoid coadministration
Dasatinib [89,90]	Inhibition CYP3A4	↑ D. exposure, ↑ QT interval	Avoid coadministration, monitor ECG
Nilotinib [89,90]	Inhibition CYP3A4	↑ N. exposure, ↑ QT interval	Avoid coadministration, monitor ECG
Ponatinib [89]	Substrate CYP3A4	↓ TKI dosage	Avoid coadministration
Sorafenib [89]	Inhibition CYP3A4	No effect	Monitor QTc
Midostaurin [89]	Inhibition CYP3A4	↑ adverse reaction	Avoid coadministration, monitor QTc
Quirzatinib [89]	Inhibition CYP3A4	↑ Quirzatinib exposure	↓ dose (induc 40 mg ->20 mg)

En Sık ≠ En Çok Öldüren

İFE nedenli ölüm % 50 azaldı – son 20 yıl

1995-2000	% 44
2001-2004	% 28



Epidemiology and Outcome of Fungemia in a Cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031)

Clin Infect Dis. 2015;61(3):324-331. doi:10.1093/cid/civ293

Flukonazol kullanımı flukonazol dirençli izolatların artışına neden oldu.

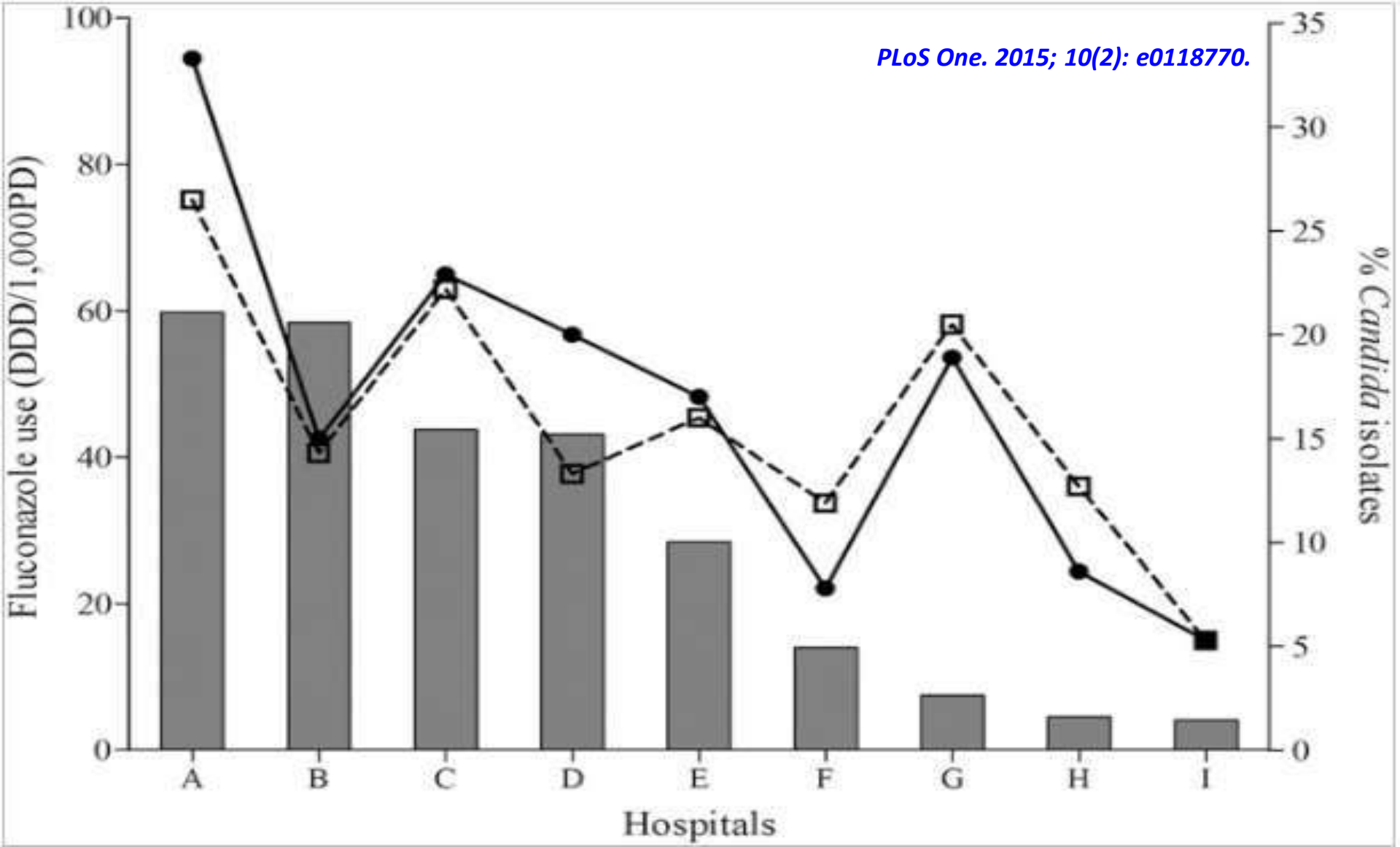


Table 1. Inherited and acquired resistance reported among pathogenic fungi infecting patients with hematological malignancies.

Fungus	Inherent resistance	Acquired resistance
	Yeasts	
Candida spp.		
C. albicans	None	Fluconazole, echinocandins
C. parapsilosis	Echinocandins (?)	Fluconazole
C. tropicalis	None	Fluconazole, echinocandins
C. glabrata	Triazoles	Echinocandins
C. krusei	Triazoles	Echinocandins
C. lusitaniae	Amphotericin B	Fluconazole, echinocandins
C. guilliermondii	Fluconazole, echinocandins	
C. auris	Azoles, amphotericin B	Echinocandins
Non-*Candida* yeasts		
Trichosporon spp.	Echinocandins amphotericin B None	Fluconazole
Saccharomyces Malassezia spp.	Echinocandins	Fluconazole
Geotrichum	Echinocandins	
Rhodotorula	Triazoles	
Pichia	Fluconazole	
	Molds	
Aspergillus spp.		
A. fumigatus	Fluconazole	Voriconazole, isavuconazole
A. terreus	Fluconazole, amphotericin B	Voriconazole, isavuconazole
A. flavus	Fluconazole, amphotericin B	Voriconazole, isavuconazole
A. nidulans	Fluconazole, amphotericin B	Voriconazole, isavuconazole
Mucorales	Fluconazole, voriconazole	
Hyalohyphomycetes *Fusarium solani* *Scedosporium* spp. *Lomentospora prolificans*	Echinocandins and variably resistant to amphotericin B and triazoles Panresistant*	

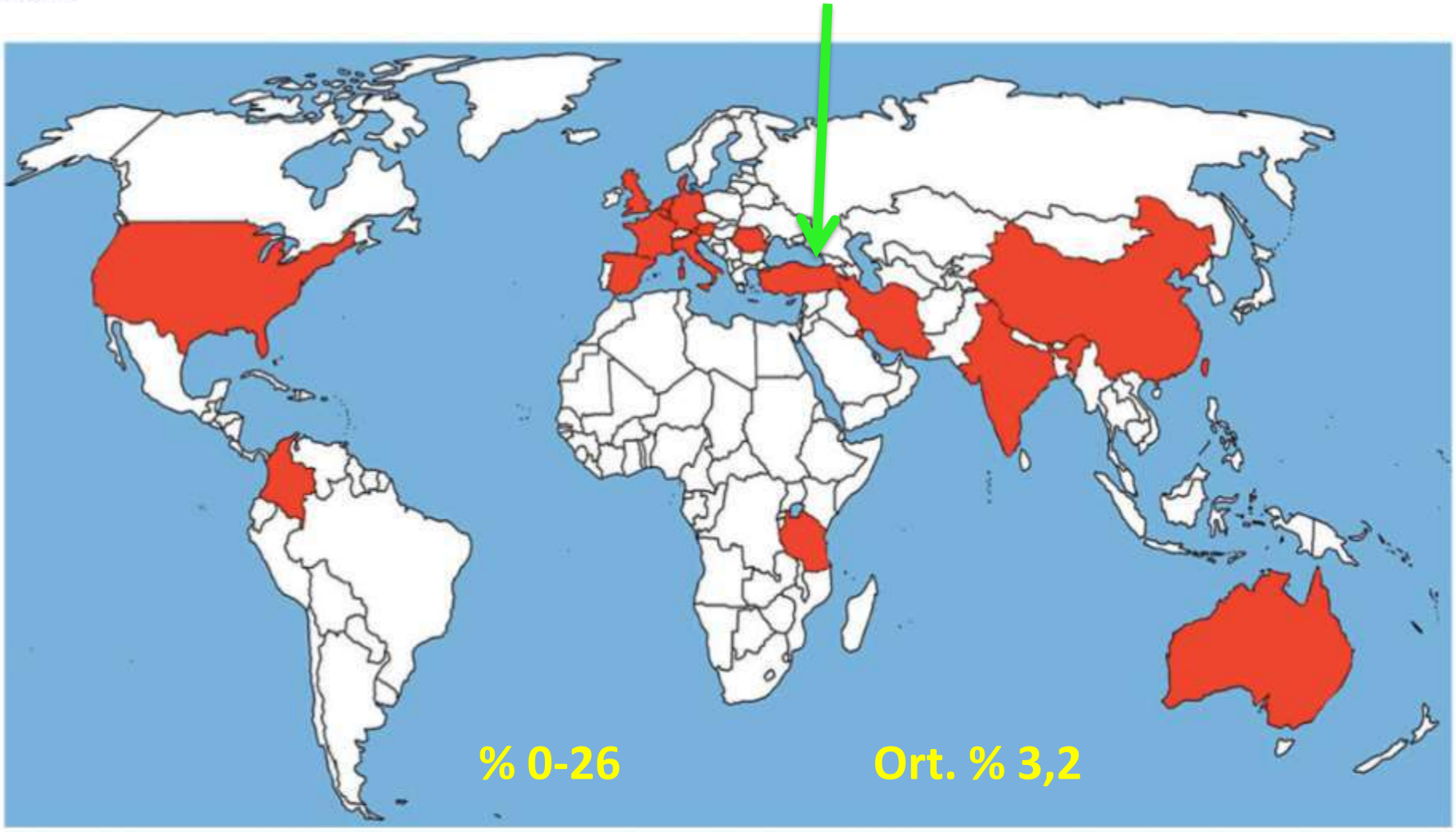
*Panresistant: Consistently resistant to all 4 major classes of systemic antifungal agents: triazoles, polyenes, echinocandins, and fluoropyrimidines.

Gamaletsou MN et al. Turk J Hematol 2018;35:1-11

First determination of azole resistance in *Aspergillus fumigatus* strains carrying the TR34/L98H mutations in Turkey

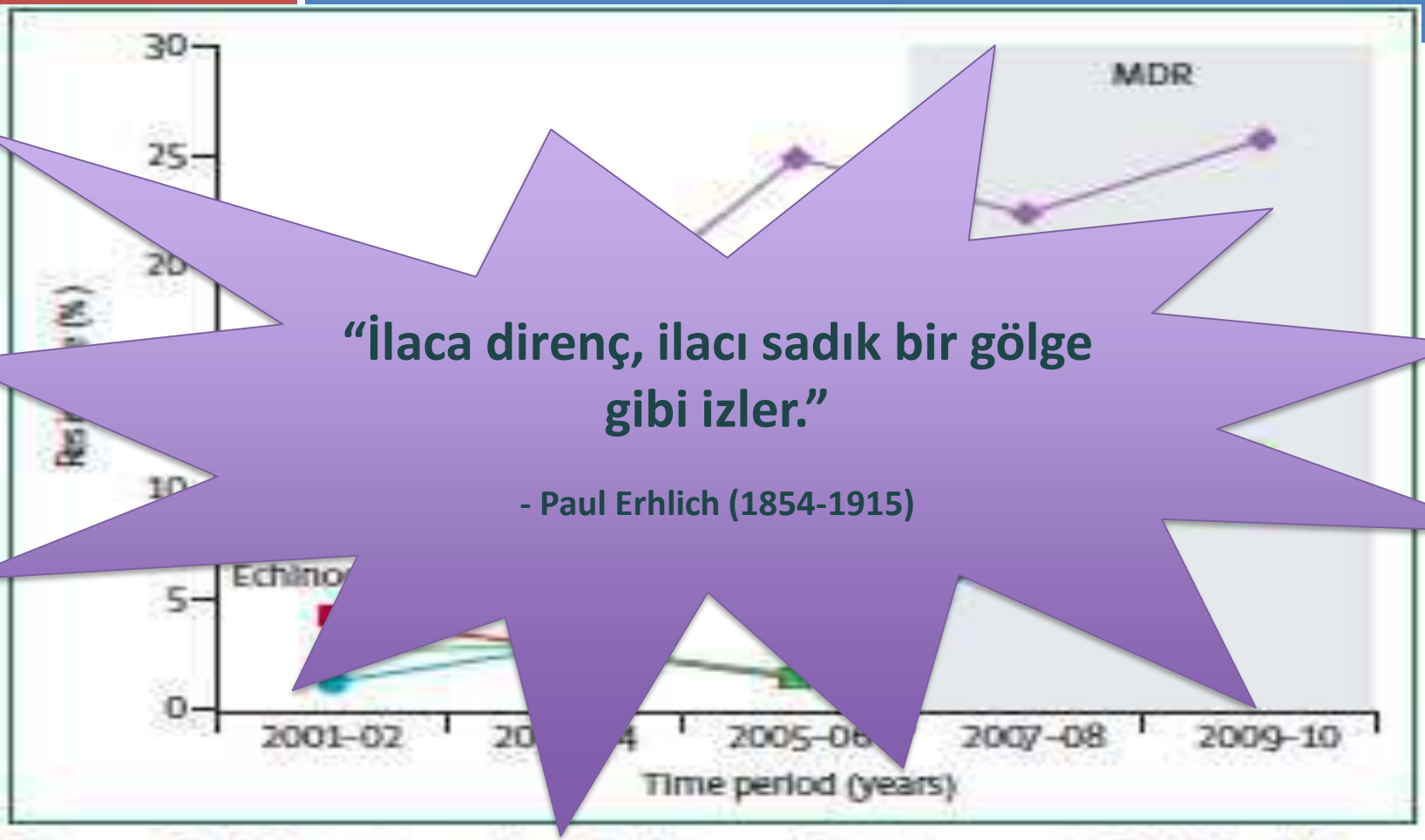
J Infect Chemother 2015;21:581e6.

Gülşah Ece Özmerdiven, Seçil Ak, Beyza Ener, Harun Ağca, Burcu Dalyan Cilo, Berrin Tunca, Halis Akalın



Verweij PE et al.CID 2016;62(3):362–8

Figure 1. Shaded areas show countries that have reported the TR_{34}/L98H and TR_{46}/Y121F/T289A resistance mechanism in clinical or environmental *Aspergillus fumigatus* isolates.



“İlaca direnç, ilacı sadık bir gölge gibi izler.”

- Paul Erhlich (1854-1915)

Figure 3: Parallel rise in azole and echinocandin resistance in *Candida glabrata* bloodstream isolates over a 10-year period, showing emergence of multidrug-resistant strains

Ekinokandin dirençli suşların % 36’sı flukonazole de dirençli – *C.glabrata*

Pham CD et al.. Antimicrob Agents Chemother 2014; 58:4690–6.
Perlin D et al.Lancet Infect Dis 2017; 17: e383–92

- Kronik granülomatöz hastalık
- GVHH ile birlikte Allo nakil
- İndüksiyon tedavisi alan MDS
- İndüksiyon tedavisi alan AML
- Akciğer veveya kalp nakli
- İnce barsak nakli
- Karaciğer nakli
- GVHH olmayan allo nakil
- Konsolidasyon tedavisinde AML

- ALL
- Kalp nakli
- KLL
  MDS
- MM
- Akut alevlenmede KOAH
- AIDS
- NHL

- Otolog kök hücre nakli
- Böbrek nakli
- Solid organ tümörleri
- Otoimmün hastalıklar

RİSK FAKTÖRLERİ

+ TANI

- Kültür / histopatoloji
- Seroloji
- Moleküler
- Radyoloji
- Klinik

- ZAMANINDA

  Yapmak

  Sonuç almak

- KOMBİNE DEĞERLENDİRMEK

Tanıda Serolojik ve Moleküler Yöntemler

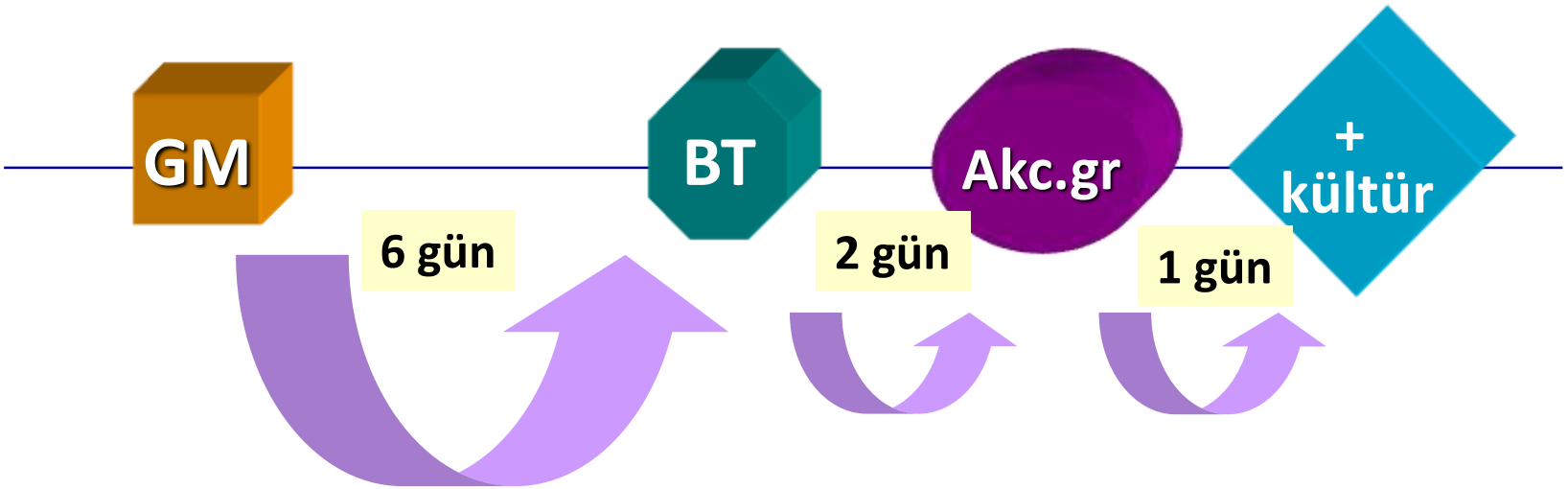
Mantar	GM*	BG	PZR
A.fumigatus	+	+	+
Non-fumigatus Aspegillus	+	+	+
Fusarium	-	+	+
Zygomyecetes	-	-	+
Candida	-	+	+
Cryptococcus	+	+/-	+

Mennink-Kersten M Infect Dis Clin N Am 2006;20:711

Allo-HSCT'de GM Testi

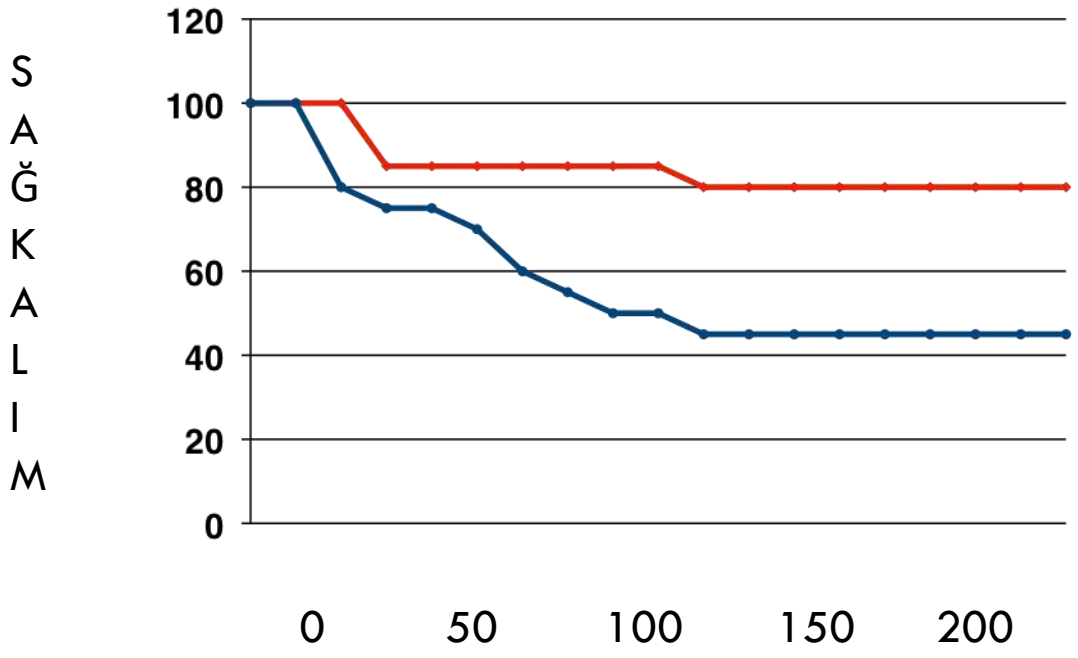
Maertens et al. JID 2002;186:1297.

Antijenemi ile diğer tanısal testler arasındaki zaman ilişkisi



Pulmoner Aspergilloz'da Sistematik CT

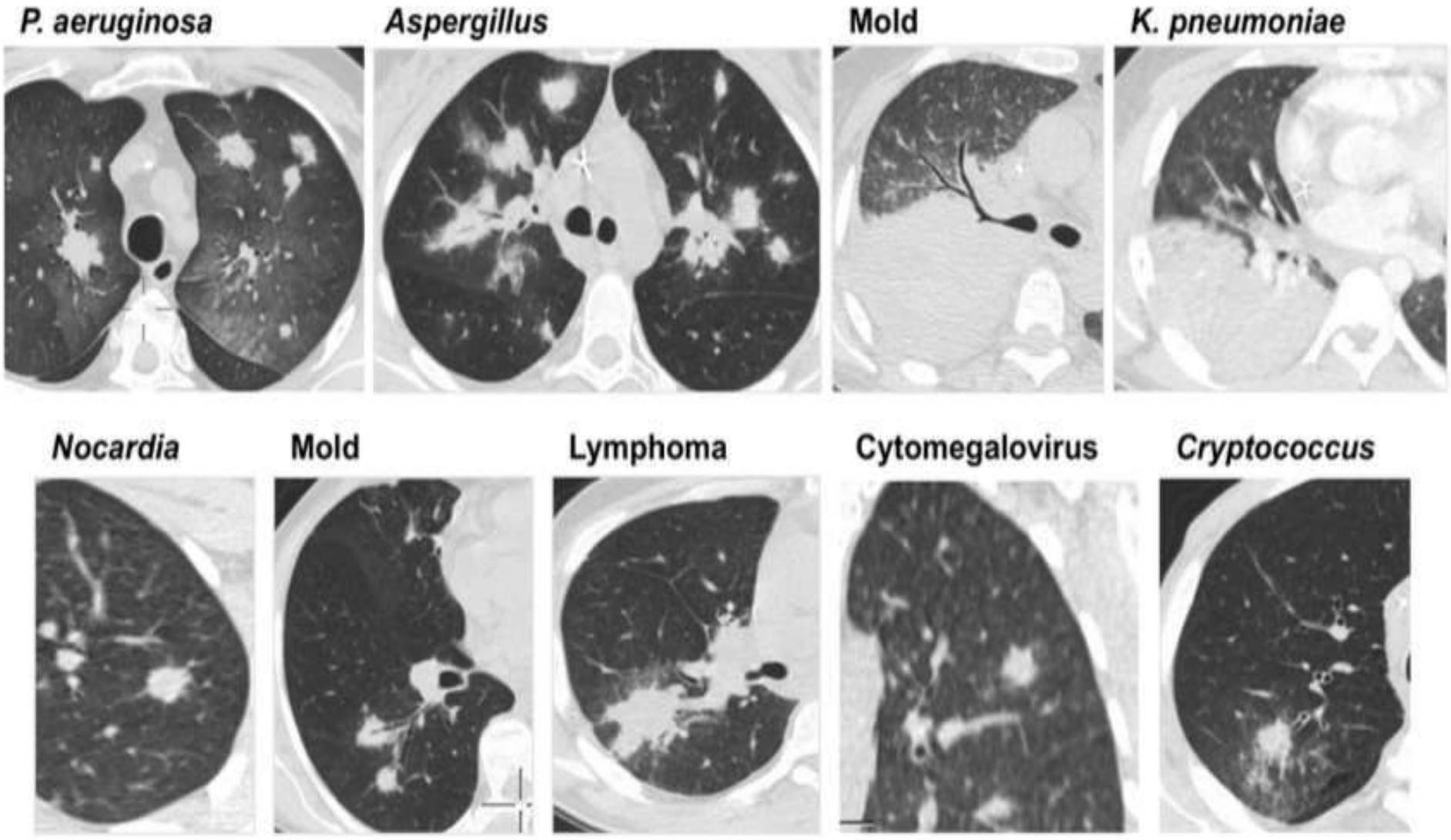
CAILLOT et al. J Clin Oncol 1997



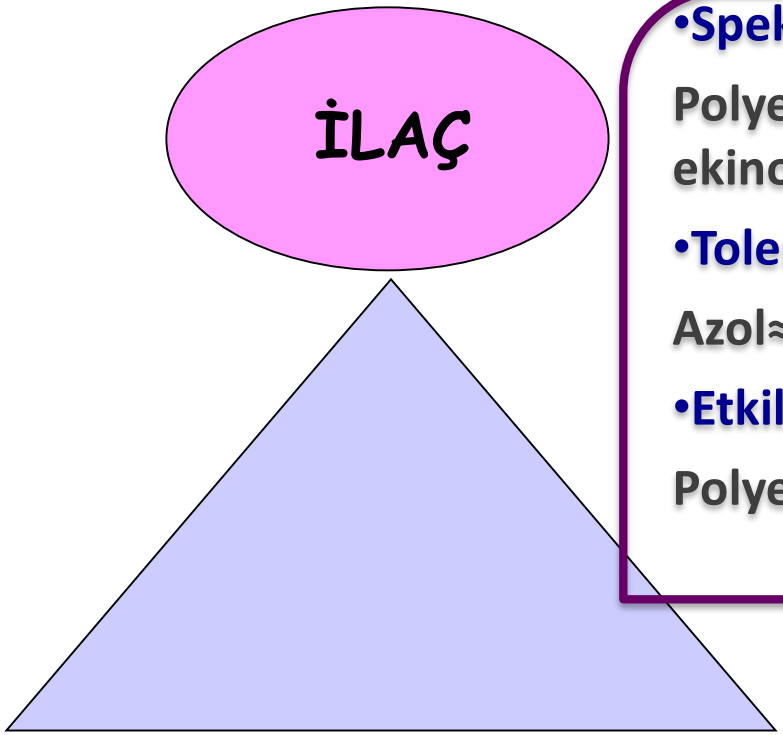
Sistematik CT-scan

Endikasyonla CT-scan

İnvazif Aspergilloz'da BT Bulguları



Antifungal Tedavi Seçme Kriterleri



İLAÇ

PATOJEN

KONAK VE TEDAVİ

- **Spektrum-etkinlik**

  Polyen ≈ azoller > ekinokandin

- **Tolerabilite**

  Azol≈ ekinokandin>polyen

- **Etkileşim**

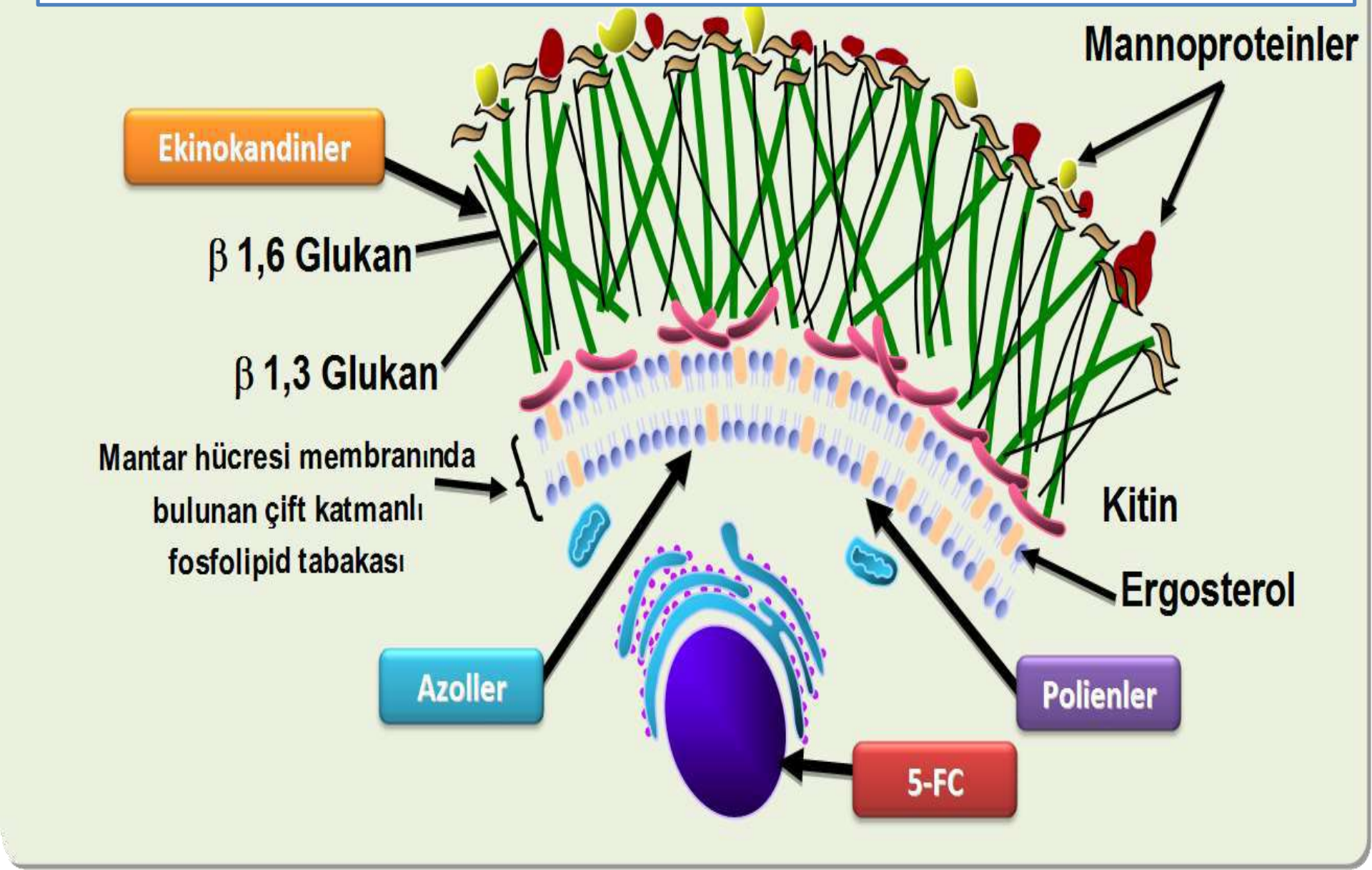
  Polyen>Ekinokandin>azol

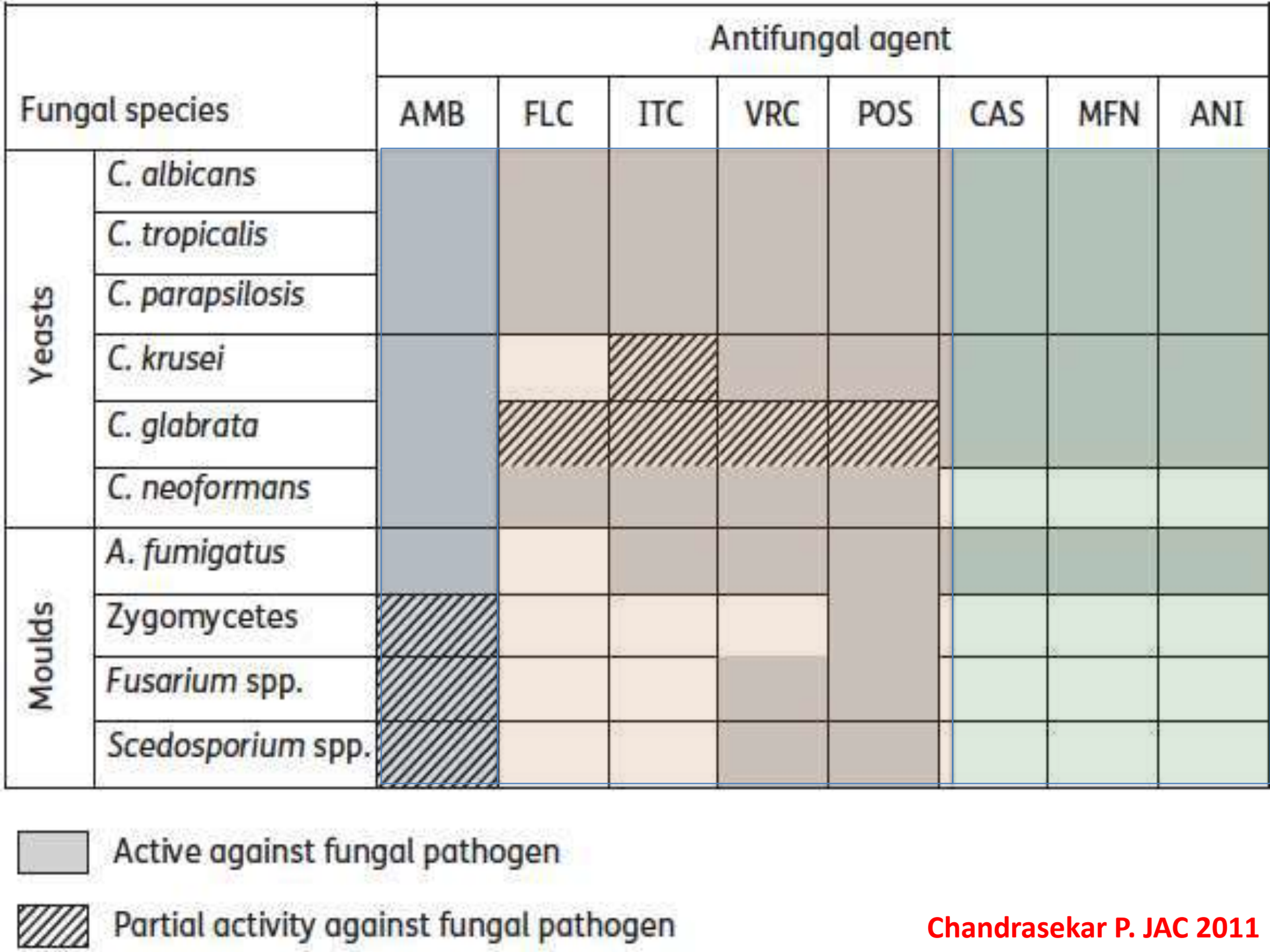
- **Epidemiyolojik özellikler**
- **Önceden aldığı ilaçlar**
- **Azol aldı ise ekinokandin öncelenmeli**

- **KC , böbrek, barsak disfonsiyonu**

Etki Mekanizması

Ergosterol tüm fungal hücre membranlarında bulunur.





Chandrasekar P. JAC 2011

L-AMB

- 1993'den bu yana kullanılıyor.
  - KAMB - 1959
- Sıralama değişse de halen en çok kullanılan AF biri.
  - Geniş spektrum
  - Etkinlik
  - Tolerabilite
  - Kombinasyon tedavilerinin ideal partneri
    - Özellikle ekinokandinler ile sinerjistik etki gösteren immunolojik özelliklere sahiptir.
  - TDM gerek yok.
  - Yan etki
  - İlaç etkileşimi sıkıntısı yok
  - Anti-biyofilm etki
  - İn-vivo ve in vitro önemli sıklıkta direnç gelişme riski yok.

Aversa F et al.Journal of Chemotherapy, 29:3, 131-143

Ekinokandinler

- IV verilir.
- Uzun yarı ömür
- SSS penetrasyonu kötü
- İnfüzyon ilişkili toksitite çok az
- İlaç etkileşimi ve yan etki açısından güvenilir.
- Diğer AF ile kombinasyon imkanı (AMB ve Azoller)
  - Hayvan çalışma veriler sinerjistik etki
- Kaspofungin, Anidulofungin, Mikafungin

- Hızlı fungisidal
- Uzun postantifungal etki

  Konsantrasyona bağlı aktivite
- Doza bağlı lineer FK etki
- *C.albicans* diren. % 2-3
- *C.glabrata* % 3-13
- Anti-biyofilm , anti-sitokin ve anti-kemokin aktivitesi

Azoller

- Geniş etki spektrumu
  - Maya küfler
- Konsantrasyon bağımsız aktivite
- Etkinlik için EAA/MİK önemli
- İnvazif aspergilloz tedavisinde vadi düzeyi önemlidir
  - Vorikonozol ve posakonazol 1-2 ɣg/ml
- İlaç seviyesi takibi – *"therapeutic drug monitoring"*-TDM

Azollerde Plazma Hedef Seviyeleri TDM

ECIL - 6

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;*

Corrado G & Anna P (2016) : An update on the safety and interactions of antifungal drugs in stem cell transplant recipients., Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2017.1273900

Triazoller ve P450 sitokrom enzimleri arasındaki etkileşim

	CYP3A		CYP2C9		CYP2C19		P-gp	
	İnhibitör	Substrat	İnhibitör	Substrat	İnhibitör	Substrat	İnhibitör	Substrat
FLU	++	0	++	0	+	+	0	0
İTRA	+++	+++	+	0	0	0	+++	++
VORİ	++/+++	+	+	0	+++	+++	0	0
POSA	++	0	0	0	0	0	++	+
İSAVU	+/++	++	0	0	0	0	+	0

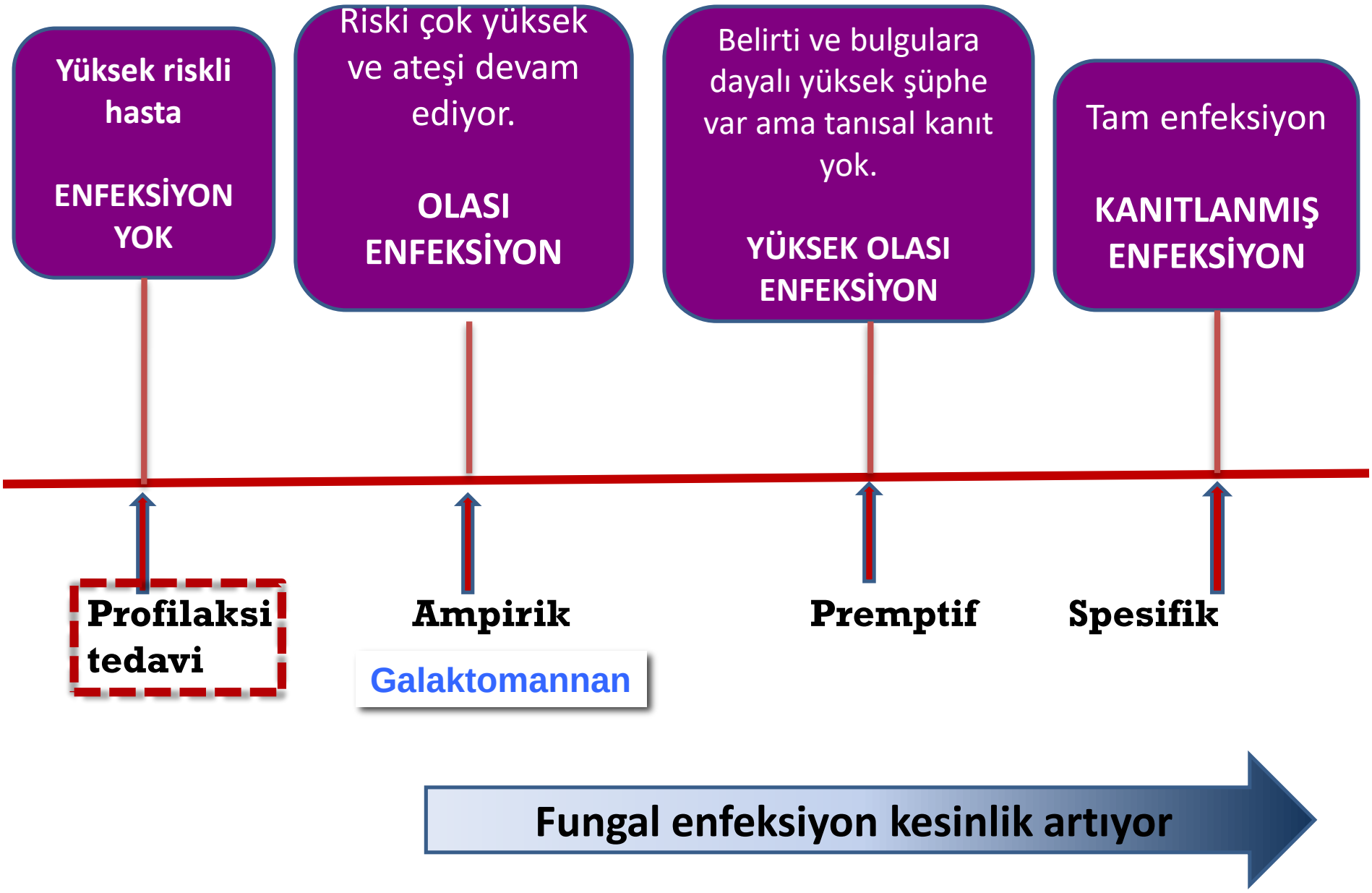
+, zayıf; ++, orta; +++,potent etkileşim

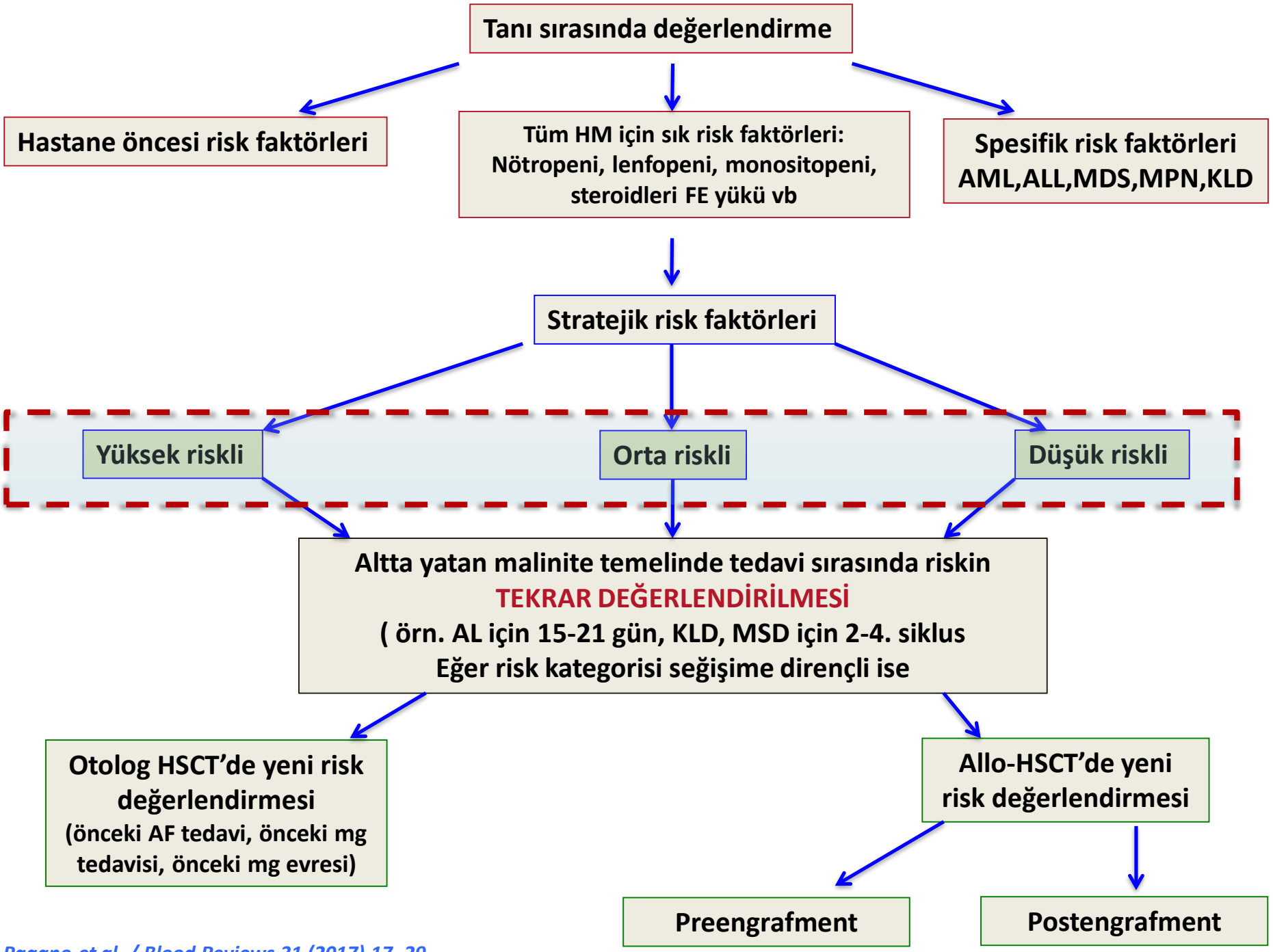
Table 1 Summary guidance for antifungal dosing in different critically ill patient subpopulations

	ARC	AKI	RRT	ALF
Amphotericin	Unchanged	Unchanged	Unchanged	Unchanged
Fluconazole	Increase	Decrease	Increase	? Unchanged
Voriconazole	TDM	TDM	TDM	TDM
Itraconazole	TDM	TDM	TDM	TDM
Posaconazole	TDM	TDM	TDM	TDM
Caspofungin	Unchanged	Unchanged	Unchanged	Decrease
Micafungin	Unchanged	Unchanged	Unchanged	Unchanged
Anidulafungin	Unchanged	Unchanged	Unchanged	Unchanged
Flucytosine	TDM	TDM	TDM	TDM

AKI acute kidney injury, *ALF* acute liver failure, *ARC* augmented renal clearance, *RRT* renal replacement therapy, *TDM* therapeutic drug monitoring

İFE Tedavi Stratejileri





L. Pagano et al. / Blood Reviews 31 (2017) 17–29

Yüksek riskli : **İFE insidansı > % 10**	• Nötrofil <0.1 × 109/L - >3 hf veya <0.5 × 109/L - >5 hf • Unrelated, mismatched veya kord kanından HSCT • GVHD • Kortikosteroid >1 mg/kg prednizona eşit ve nötrofil <1 × 109/L - >… • Kortikoster… …nf • Yüksek doz si… • Flu… …şük grade … • Alemtuzu… …KLveya düşük gra… • ALL • AML
Orta derece riskli: **İFE insidansı ~% 10**	• Nötropeni 0.1–0.5 × 1…L - 3–5… • Nötropeni 0.1–0.5 × 10…L for <3 h – lenfopeni ile birlikte (lenfosit <0.5 × 109/L)
Düşük risk: **İFE insidansı ~ % 2%**	• PBSC otolog • HSCT lenfoma

Nötropenik hastada

İFE insidansı ≥ % 10 ise

PX verilir.

**Fleming S et al Intern Med J, 44(12b), 1283-1297 (2014)*

***NCCN Guidelines Version 1.2018 Prevention and Treatment of Cancer-Related Infections*

Profilaksi Vereceğim….

- **Epidemiyolojik eğilimler**
  - Etken, direnç durumu bilinmeli
  - Risk faktörleri
- **Enfeksiyon riskinin süresi**
- **İlacın veriliş yolu**
  - Mukozit, grade 4 GVHD, ileus, nötropenik enterokolit, malabsorbsiyon – IV
- **Toksitite ve ilaç etkileşimleri**
- **Maliyet**

Slavin MA et al. Intern Med J 2008;38:468

Profilaksi Vereceğim…

- **Profilaksi veren merkezler daha agresif olmalı**
  - Direnç durumunun takibi
  - *Breakthrough* İFE tanısal girişimlerin kullanımında
  - Küflere etkili ajanlar GM suprese edebilir.
    - İA tanısında geçikme
- **İlaç düzeyinin takibi (TDM) kimlere ?**
  - Mukozit, bulantı, kusma
  - Tedavi başarısızlığı

Slavin MA et al. Intern Med J 2008;38:468

Profilaksi

- **Primer**
  - Universal profilaksi
  - Hedeflenmiş profilaksi
    - AML - Konsolidasyon KT
    - ALL- AML benzeri KT uygulananlar
    - Allo-HSCT
      - Kord kanı / haploidentilak donor
        - » Enfeksiyon riski yüksektir
        - » Agresif ve uzun profilaksi – engraftment ve postengraftment
- **Sekonder**

Risk Faktörleri HM

Fleming S et al Intern Med J, 44(12b), 1283-1297 (2014).

Candida spp. Enfeksiyonları

- Yoğun indüksiyon rejimi alan hastalar (GİS hasarı)
- Geniş spektrumlu AB
- SVK

Aspergillus spp. Enfeksiyonları

- İlerlemiş/ refrakte AML
- Yüksek riskli MDS
- Remisyon için çoklu KT ihtiyacı
- Demir yükü – çoklu kan TX sonucu
- KT öncesi kronik nötropeni
- Tedaviden önce aspergillosis olması
- Son CMV enfeksiyonu ve gansiklovir kullanımı

İFE Risk Faktörleri
KİT

Pre-engraftment dönemde → **Candida > Aspergillus**

Aspergillus spp **enfeksiyon riskinin artıran durumlar:**

- **Önceden Multipl KT**
- **Fe yükü – çoklu kan TX**
- **Önceden İA öyküsü**
- **TX sonrası engraftment başarısızlığı / geçikmesi – umblikal kord TX sık görülür.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Prevention and Treatment of Cancer-Related Infections

AF Profilaksi yok

Maya profilaksisi

KÜF profilaksisi

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK (See FEV-2)	ANTIMICROBIAL PROPHYLAXIS d,e,f,g,h,i
Low	• [illegible]		[illegible]
Intermediate	• Autologous HCT • Lymphoma[c] • Anticipated neutropenia 7–10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia (>20 mg daily) • Anticipated neutropenia greater than 10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia depending on risk (See INF-3, INF-4, INF-5)

KEY: CLL = chronic lymphocytic leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus, PCP = pneumocystis pneumonia

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.

[b] In high-risk patients, additional prophylaxis may be necessary; for example, consider penicillin and trimethoprim/sulfamethoxazole (TMP/SMX) for allogeneic HCT recipients with chronic GVHD.

[c] This is a heterogenous disease. Therefore, treatment modalities and the type of malignancy affect risk level.

[d] Pneumocystis prophylaxis (See INF-6).

[e] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.

[f] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.

[g] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions.

[h] Although data support levofloxacin prophylaxis for low- and intermediate-risk patients, the panel discourages this practice in low-risk patients because of concerns about antimicrobial resistance; however, it can be considered in intermediate-risk patients.

[i] For patients who are intolerant to fluoroquinolone, consider TMP/SMX or an oral third-generation cephalosporin (category 2B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of patients with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	ANTIFUNGAL PROPHYLAXIS[f,l]	DURATION
INTERMEDIATE TO HIGH	ALL	Consider: • Fluconazole[m] or Micafungin[n] • Amphotericin B products[o] (category 2B)	Until resolution of neutropenia
	MDS (neutropenic) AML	Consider: • Posaconazole[m] (category 1) [n] Fluconazole,[m] Micafungin,[n] or B products[o] (all category 2B)	
	Auto	or Micafungin[n] (both c gory 1)	
	Auto		N/A
	Allo See	or Micafungin[n] (both category 1) [n] Posaconazole,[m] or Amphotericin B category 2B)	Continue during neutropenia[p]
	Significant GVHD[k] See Antipneumocystis Prophylaxis (INF-6)	Consider: • Posaconazole[m] (category 1) • Voriconazole,[m] Echinocandin, or Amphotericin B products[o] (all category 2B)	Until resolution of significant GVHD

Profilaksi süresi

KEY: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndromes, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
[f] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[l] Mucositis is a risk factor for candidemia in patients with hematologic malignancies and HCT recipients not receiving antifungal prophylaxis.
[k] Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy.
[l] There is substantial variability in practice among NCCN Member Institutions. Physicians need to take into account local susceptibility patterns.
[m] Itraconazole, voriconazole, and posaconazole are more potent inhibitors of hepatic cytochrome P450 3A4 isoenzymes than fluconazole and may significantly decrease the clearance of several agents used to treat cancer (eg, vincristine).
[n] All three agents in the class (micafungin, caspofungin, and anidulafungin) are considered by many to be interchangeable.
[o] A lipid formulation is generally preferred based on less toxicity.
[p] Some studies continue treatment up to day 75.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of patients with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

Maertens MA et al. JAC, Volume 73, Issue 12, 1 December 2018, Pages 3221–3230

Table 3. ECIL recommendations on primary antifungal prophylaxis in adult patients with AML and MDS undergoing intensive remission-induction chemotherapy[a]

Antifungal agent	Grading	Comments
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	A-I	Recommended if baseline incidence of mould infections is high. Given the increased absorption of the tablet, it is likely that the need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis).
Fluconazole 400 mg q24h	B-I	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.
Itraconazole oral solution 2.5 mg/kg q12h	B-I	Recommended if baseline incidence of mould infections is high. May be limited by drug–drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations.
Voriconazole 200 mg q12h	B-II	Recommended if baseline incidence of mould infections is high. It is recommended to monitor serum drug concentrations.
All echinocandins	C-II	Insufficient data on efficacy and tolerability.
Liposomal amphotericin B	C-II	Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability.
Lipid-associated amphotericin B	C-II	Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability.
Aerosolized liposomal amphotericin B (10 mg twice weekly)	B-I	Only when combined with fluconazole 400 mg q24h.
Amphotericin B deoxycholate	A-II against	
Aerosolized amphotericin B deoxycholate	A-I against	

[a]Primary antifungal prophylaxis might be considered during intensified consolidation therapy (see text).

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

Maertens MA et al. JAC, Volume 73, Issue 12, 1 December 2018, Pages 3221–3230

Table 4. ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: pre-engraftment period

	Pre-engraftment risk of mould infections	
Antifungal agent	low	high
Fluconazole 400 mg q24h	A-I	
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	B-II	B-II
Itraconazole oral solution 2.5 mg/kg q12h	B-I	B-I
Voriconazole 200 mg q12h	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h	C-III	B-II
Fluconazole 400 mg q24h		A-III against

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

Maertens MA et al. JAC, Volume 73, Issue 12, 1 December 2018, Pages 3221–3230

Table 5. ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: post-engraftment period

Antifungal agent	High risk GvHD
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	A-I[a,b]
Itraconazole oral solution 2.5 mg/kg q12h	B-I[b]
Voriconazole 200 mg q12h	B-I[b]
Micafungin 50 mg q24h	C-II
Caspofungin and anidulafungin	no data
Liposomal amphotericin B	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h	no data
Fluconazole 400 mg q24h	A-III against

[a]No difference with placebo was seen in patients with chronic GvHD.[59]
[b]It is recommended to monitor serum drug concentrations.

Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guidelinec

Sekonder Profilaksi

- Önceden başarılı olarak tedavi edilmiş **İA öyküsü** olan ✚ takip eden bir immunosupresyon riski olan bir dönem
  - Allojeneik HSCT (erken faz), otolog yapılacak ise
  - Ağır nötropeniye yolaçacak kemoterapi (< 500/Ml ve en az 7 gün sürecek),
  - yoğun kronik GVHD
  - T hücre supresyon tedavisi (steroid)

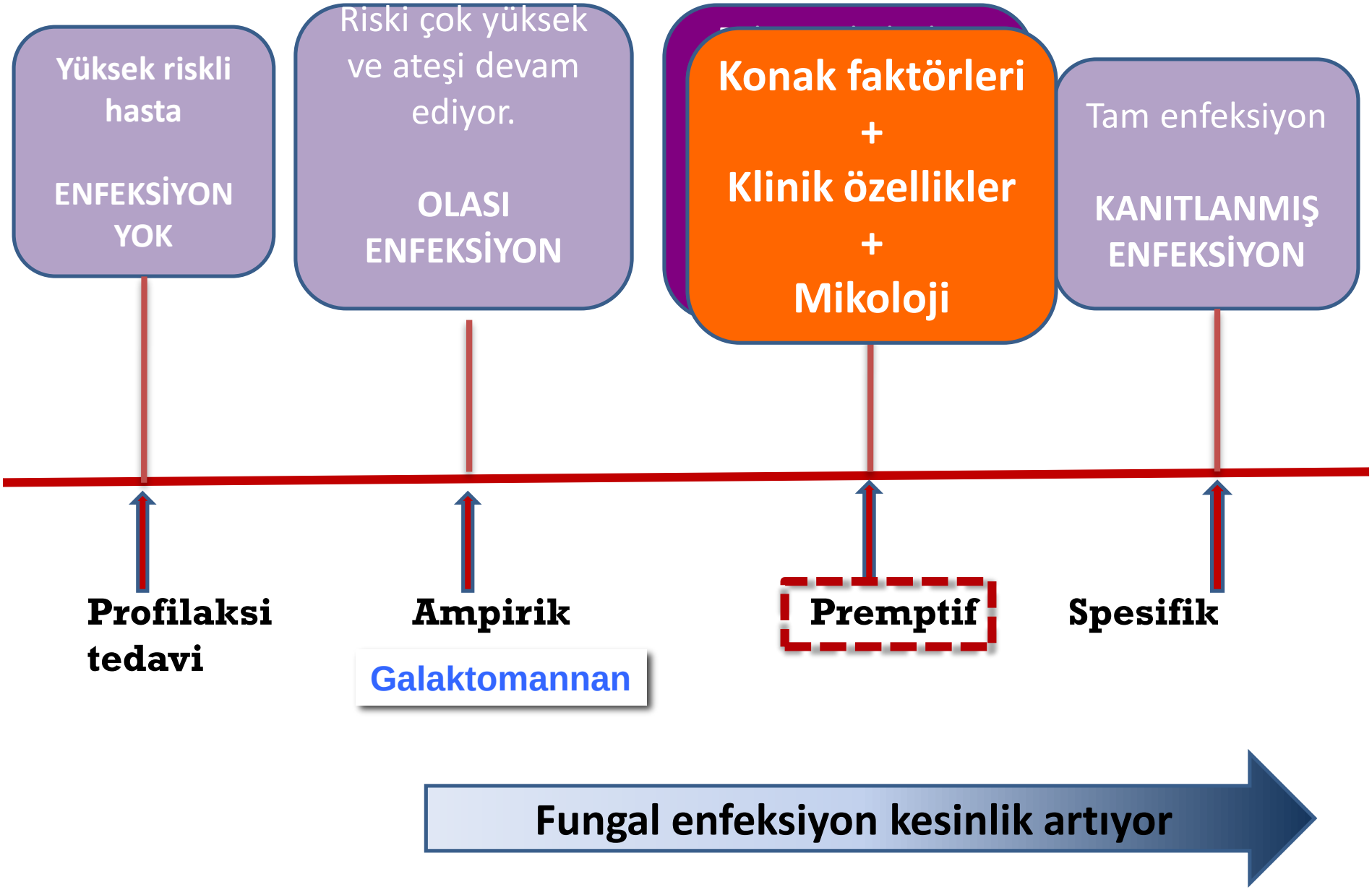
- **Küf aktif sekonder profilaksi tüm immunsupresyon periyodu boyunca devam etmelidir.**

Table 36
Secondary prophylaxis

Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guidelinec

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

İFE Tedavi Stratejileri



Preemtif Tedavi NEDİR?

- **Yüksek riskli hasta** ✚
  - Klinik tablo (ateş vd)
  - Biolojik göstergeler (GM, BG)
  - BT

?

Preemtif Tedavi AMAÇ

- **Gizli İFE saptamak ve tedavi etmek**
- **Maliyet , yan etki ve toksititeyi düşürmek**

Ampirik tedavi, preemptif tedaviye göre İFİ* insidansını ve mortaliteyi anlamlı olarak azaltır.[1]

Kanıtlı/olası İFİ insidansı[1]

İnvazif fungal hastalığa bağlı mortalite insidansı[1]

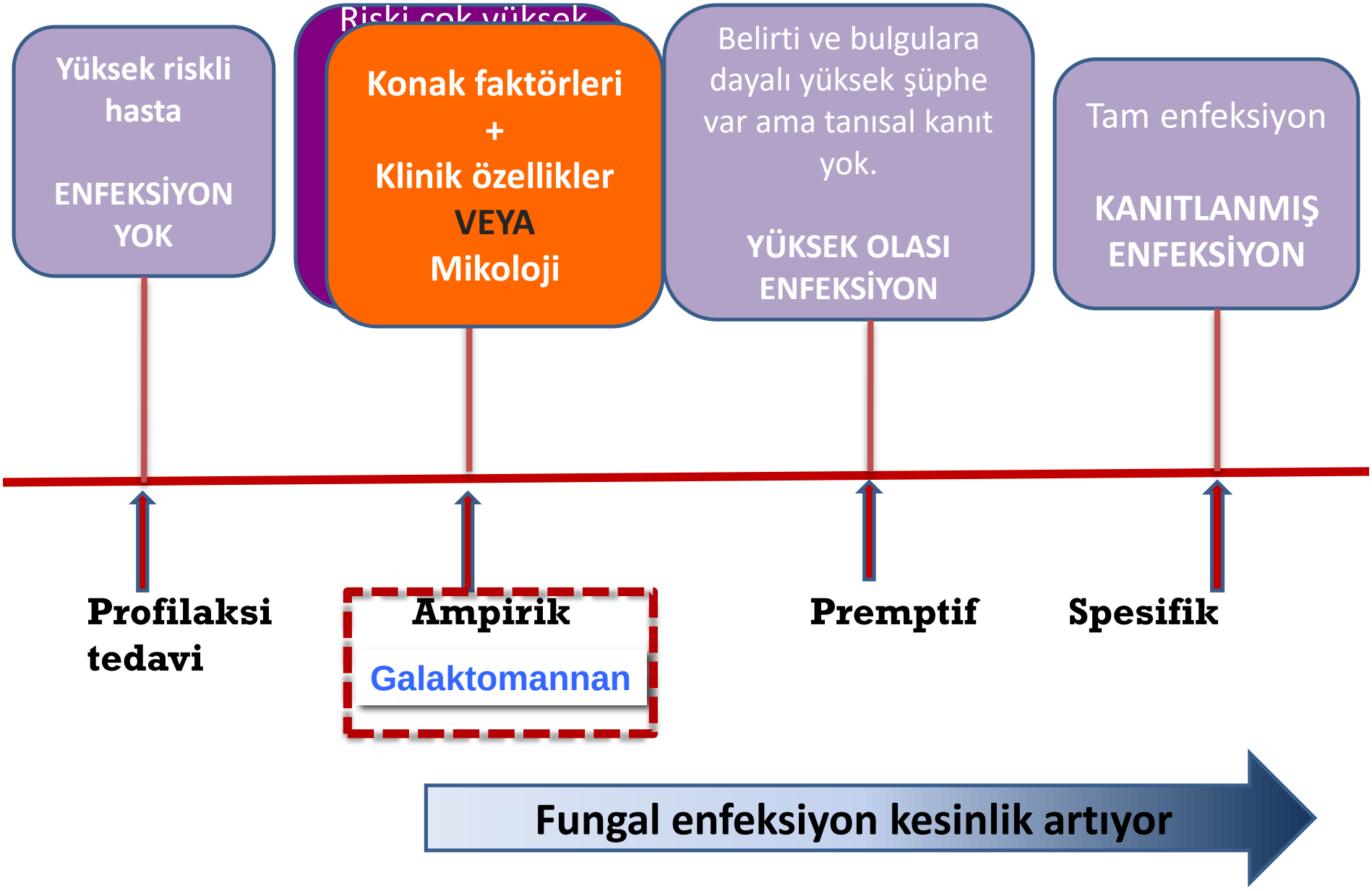
Preemtif tedaviyi

ECIL III 2009 derecelendirilmedi.

- **Özellikle uzamış nötropenide sıkıntılıdır.**
- **Antifungal tedaviye başlama kriterleri standart değil**
- **İki çalışma sonuçları değişken**

Pagano L et al. Haematologica. 2011 Sep;96(9):1366-70

İFE Tedavi Stratejileri



NCCN Guidelines Version 1.2018
Prevention and Treatment of Cancer-Related Infections

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Discussion

RESULTS OF DAILY MONITORING

- Clinically stable or improving
- Fever decreasing

→ No change in initial empiric regimen
- Modify regimen based only on new clinical or microbiologic data
- Empiric regimen should be continued at least until ANC is ≥500 cells/mcL and increasing

- Persistently febrile
- Otherwise clinically stable

→ (same)

- Not responding/ clinically worsening
- Persistently febrile
- Persistent bacteremia

→
- Broaden coverage based on clinical and microbiologic data to include other organisms not covered by initial empiric regimen
- Consider imaging studies and further microbiological testing
- Consider adding G-CSF or GM-CSF (category 2B)
- ID consult

FOLLOW-UP THERAPY

Documented infection → See Duration (FEV-11)

Fever resolved, unknown origin
- Neutrophils ≥500 cells/mcL → Discontinue therapy
- Neutrophils <500 cells/mcL[x] → Continue current regimen until neutropenia resolves[y]

→
- Consider antifungal therapy with activity against molds for fever continuing ≥4 days of empiric antibiotic therapy[z,aa]
- Duration of therapy depends on clinical course, neutropenia recovery, toxicity, and opinions of ID consultants

Israr Eden Nötropenik Ateş

- **Geniş spektrumlu antibiyotiğe rağmen ≥ 4 gün ateş devam ederse AF eklenir.**
  - Ampirik antifungal tedavi eklemek zamanı **invaziv küf enfeksiyonları riski** ile değişir,
  - Genel olarak 4-7 gün
  - Küf enfeksiyonu için yüksek riskli hastalarda (> 10 gün nötropeni, yüksek doz KST, allo KİT)

NCCN Panel, küf aktif ajanlarla profilaksi almadıkça, 4 gün sonra ampirik antifungal ajanların eklenmesini önermektedir.

NCCN Guidelines Version 1.2018 Prevention and Treatment of Cancer-Related Infections

Israr Eden FN

- **Küf aktif antifungal ekle**
  - **Vorikonazol/ posakonazol profilaksisi alıyorsa**
    - Hastada İFE için yeterli tanısal işlemlere rağmen klinik bulgu yok, GM (-), posakonazol ve vorikonazol hedef seviyelerde ise oral AF profilaksi devam eder.
    - Klinik kötüleşme var ise IV antifungal tedaviye geç (AIII).

W. J. Heinz Ann Hematol (2017) 96:1775–1792

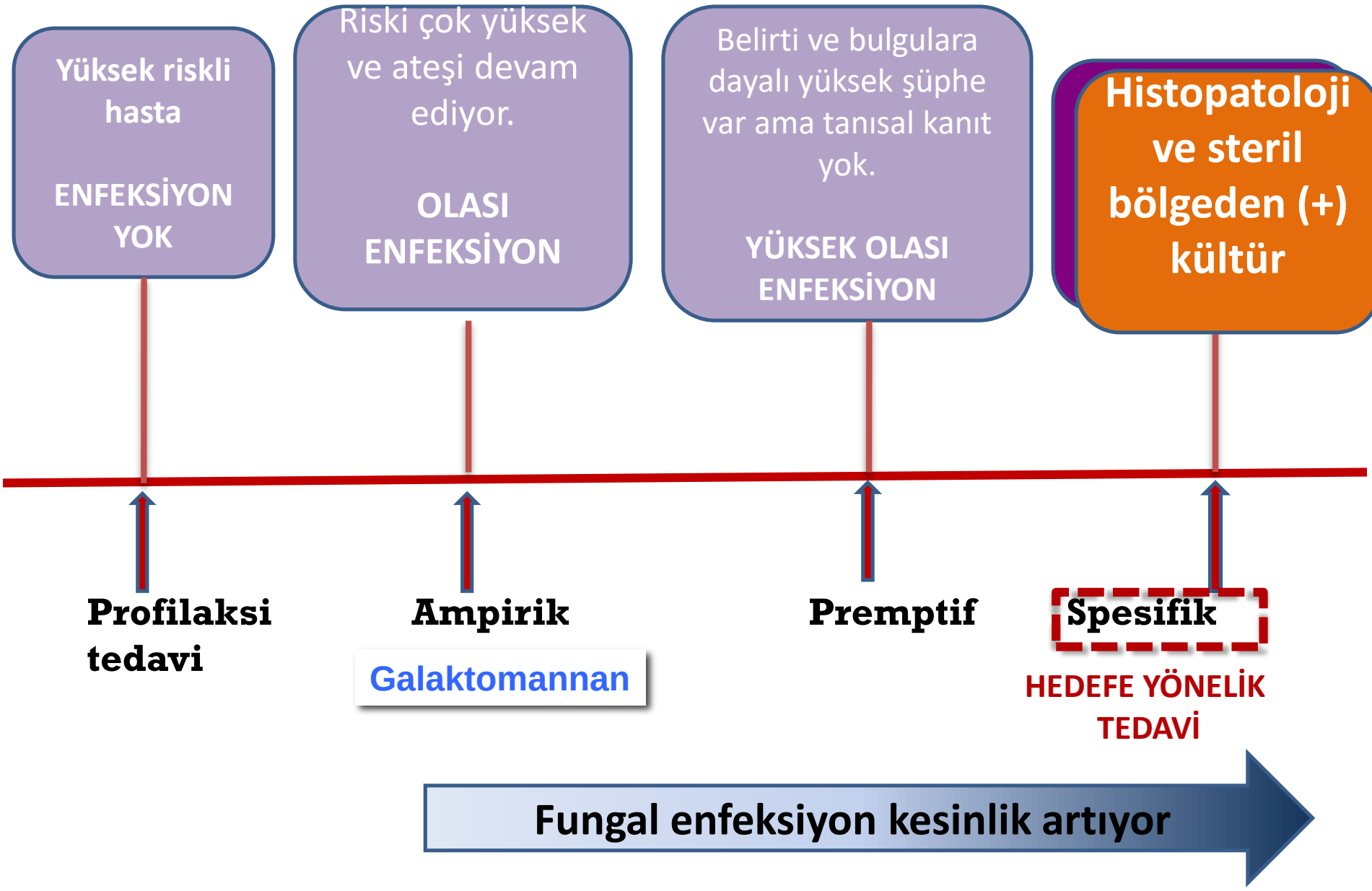
Table 29
Fever-driven ('empiric') approach

Population	Intention	Intervention	SoR	QoE	Comment
Chemotherapy for haematological malignancies or HSCT, neutropenia <500/μL ≥96 h, fever (>38C), and parenteral broad spectrum antibacterial therapy ≥96 h (some centres consider 48 h)	Reduction in the incidence of IA and/or related mortality	Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	A	I	Caspofungin was associated with a significantly higher rate of survival than L-AmB (subgroup analysis).
		L-AmB 3 mg/kg	B	I	Less toxicity in comparison to cAmB but more renal toxicity compared with echinocandin
		Voriconazole 6 mg/kg bid IV (oral 400 mg bid) on day 1, then 4 mg/kg bid IV (oral 200–300 mg bid)	B	II	Failed the 10% non-inferiority cut-off when compared with L-AmB, but first-line for aspergillosis. Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM
		Itraconazole 200 mg qd iv	C	II	Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM
		ABLC 5 mg/kg qd	C	I	Infusion-related toxicity (fever, chills, hypoxia)
		ABCD 4 mg/kg	C	I	Same as above
		cAmB 0.5–1 mg/kg qd	D	I	Poor tolerance due to extreme toxicity
		Micafungin 100 mg qd	B	II	
		Fluconazole	D	II_r	No activity against *Aspergillus*

Antifungal Eklemeli miyim ?

- **Hasta antifungal tedavi almış / PX alıyorsa ve sonra FN gelişti;**
  - Flukonazol dirençli *Candida spp* (*C.krusei* veya *C.glabrata*) veya invazif küf enfeksiyonu (*Aspergillus*)
  - Dirençli kandida enfeksiyonu şüphesi varsa ➔ Ekinonokandin başla – mikafungin/kaspofungin
  - BT halo belirtisi veya GM (+) *Aspergillus* şüphesi yüksektir.
    - GM (-) olması tanısal değildir –düşük duyarlılık
  - *Aspergillus* şüphesi varsa ➔ vorikonazol gerekirse LAMB

İFE Tedavi Stratejileri



Hedefe Yönelik Tedavi

- Kanıtlı – Kesin (Proven)
- Olası enfeksiyon (Probable)

- Kandida enfeksiyonları
- Aspergillus enfeksiyonları

İnvazif Kandidiyazis
Ekinokandinler ilk Tercih

- Yakın zamanda azol kullanma
- Israrcı nötropeni
- Azol alerjisi veya AMB intolerans
- *C.krusei* veya *C.glabrata* riski yüksek ise
- APACHE skoru > 20 olan hastalar

Pappas PG Infect Dis Clin N Am 2006;20:485

IDSA 2016 İnvazif Kandidiyazis
Nötropenik Hastada Kandidemi Tedavi Önerileri

Antifungal	Öneri
Mikafungin **Kaspofungin** **Anidulofungin**	Güçlü öneri; orta kalite
LAMB	Güçlü öneri; orta kalite
Flukonazol	Zayıf öneri; düşük kalite
Vorikonazol	Zayıf öneri; düşük kalite

Table 4. ECIL-6 recommendations for initial first-line treatment of candidemia.

	Overall population	Hematologic patients
Antifungal therapy		
Micafungin[a]	A I	A II
Anidulafungin	A I	A II[b]
Caspofungin	A I	A II
Liposomal amphotericin B	A I	A II
Amphotericin B lipid complex	B II	B II
Amphotericin B colloidal dispersion	B II	B II
Amphotericin B deoxycholate[c]	C I	C II
Fluconazole[d,e]	A I	C III
Voriconazole[d]	A I	B II
Catheter removal[f]	A II	B II

[a]See warning box in European label; [b]provisional grading; [c]close monitoring for adverse event is required; [d]not in severely ill unstable patients; [e]not in patients with previous azole exposure; [f]if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended.

Tissot F et al.Haematologica 2017 Volume 102(3):433-444

Table 5. ECIL-6 recommendations for first-line treatment of candidemia after species identification.

Tissot F et al.Haematologica 2017
Volume 102(3):433-444

Candida species	Overall population		Hematologic patients	
C. albicans	Echinocandins[a]	A I	Echinocandins	A II
	Fluconazole[b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins[a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins[a]	A II	Echinocandins[a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins[c]	B II	Echinocandins	B III

[a]Same grading for anidulafungin, caspofungin, micafungin; [b]not in severely ill patients; [c]if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72 h), continuing use of echinocandin might be considered.

İnvazif Aspergillozis

Kesin bir İA tanısını koymak zordur.
EORTC / MSG tanımları sadece klinik çalışmalar için tasarlanmıştır.
Klinik karar verme için, kanıtlanmış veya muhtemel bir tanının doğrulanmasının tedavinin başlangıcını geciktireceğinden, bu tanımların zararlı bir sonucu olabilir.

Sorumlu klinisyen tarafından IA olarak kabul edilen risk altındaki herhangi bir hasta antifungal tedavi almalıdır **(AIII).**

Table 2. Recommendations for the Treatment of Invasive Pulmonary Aspergillosis.

Targeted Treatment of Invasive Pulmonary Aspergillosis in Hematologic Malignancy					
	Voriconazole	Isavuconazole	Itraconazole	Liposomal Amphotericin B	Echinocandins
ECIL-6 (61)	AI	AI	CIII	BI	CII
ESCMID (60)	AI-AII	AI-AII	CII-CIII	BII	CII-CIII
IDSA (83)	AI	AII	-	AII	AII (not recommended)
Salvage Treatment for Invasive Pulmonary Aspergillosis in Hematologic Malignancy					
	Voriconazole	Isavuconazole	Itraconazole	Liposomal Amphotericin B	Posaconazole
ECIL-6 (61)	BII	BII	CIII	BII	BII
ESCMID (60)	AII	AII	CII-DIII	BII	BII
IDSA (83)	-	-	AII	AII	AII

Table 2. Recommendations for the Treatment of Invasive Pulmonary Aspergillosis.

Combination Treatment for Invasive Pulmonary Aspergillosis in Hematologic Malignancy		
	Voriconazole + Echinocandin	Other combinations
ECIL-6 (61)	CI	CIII
ESCMID (60)	CI-CII	DIII
IDSA (83)	CII	CII

Targeted Treatment of Chronic Pulmonary Aspergillosis					
	Voriconazole	Isavuconazole	Itraconazole	Liposomal Amphotericin B	Posaconazole
ECIL-6 (61)	.	.	.	.	.
ESCMID (60)	AII	.	AII	.	BII
IDSA (83)	.	.	Preferred	.	.

İA Kombinasyon Tedavisi

ECIL III 2009

- **İlk tedavi olarak önerilmiyor** **DIII**
- **Kurtarma tedavisi**
  - Kaspofungin + Lipid AMB **CII**
  - Kaspofungin + vorikonazol **CII**
  - AMB (hepsi) + Azol veri yok

TEDAVİ - IA

REVIEW ARTICLE

A practical critique of antifungal treatment guidelines for haemato-oncologists

Topic discussed	Consensus	Conflict/unresolved issues
Combination therapy in first-line treatment	Discouraged by all guidelines (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010; Prentice et al., 2008; Slavin et al., 2008; Böhme et al., 2009; Cornely et al., 2009)	

Ann Hematol (2014) 93:13–32
DOI 10.1007/s00277-013-1867-1

ORIGINAL ARTICLE

Treatment of invasive fungal infections in cancer patients—updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

Table 2 Treatment of invasive *Aspergillus* infections in hemato-oncological patients

First-line treatment of invasive pulmonary aspergillosis	
Voriconazole	AI
Liposomal AmB	AII
Caspofungin	CII
Micafungin	CII
ABLC	CIII
Anidulafungin + voriconazole	CIII
D-AmB	EI

Ann Intern Med. 2015 Jan 20;162(2):81-9

Combination antifungal therapy for invasive aspergillosis: a randomized trial.

277 hasta, proven + probable

	(vori + anidulafungin)	vs	(Vori)
ölüm oranı	**% 16**		**% 27**
6 hf			

Antifungal Tedavi Süresi

Nötropenik dönem boyunca

Enfeksiyonun rekürrensini önleyecek ve hematojen yayılıma neden olacak tüm odakların ortadan kaldırılmasına yetecek kadar

Antifungal Fedavi Süresi

İnvaziv Kandidiyaz

• Son pozitif/ son negatif kan kültüründen itibaren 2 hafta

– Nötropenik hastada (güçlü öneri; orta kalitede kanıt)

Kateter değiştirilmediyse 3-6 gün daha uzun tedavi mortaliteyi azaltıyor

German Society of Hematology and Oncology

Pappas et al. IDSA Guideline, 2016

Antifungal Tedavi Süresi

İnvaziv Aspergilloz

- En az 6- 12 hafta
- Enfeksiyonun lokalizazyonu
- Klinik iyileşme
- Alta yatan hastalığın iyileşmesi
- Nötropeni süresine
- Saptanan lezyonlar tamamen kaybolana ya da skar halini alana kadar

Aspergillosis:IDSA Guideline CID 2016:63

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

[a]Both comments apply to the oral solution but may not apply to the solid oral formulation.

Defining breakthrough invasive fungal infection–Position paper of the mycoses study group education and research consortium and the European Confederation of Medical Mycology

Cornely OA et al. Mycoses. 2019;62:716–729.

Oliver A. Cornely[1,2,3] | Martin Hoenigl[4,5] | Cornelia Lass-Flörl[6] | Sharon C. -A. Chen[7] | Dimitrios P. Kontoyiannis[8] | C. Orla Morrissey[9] | George R. Thompson III[10] | for the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM)

Term	Definition
Persistent IFI	IFI unchanged from baseline, may precede treatment success
Refractory IFI	IFI with worsening or new attributable clinical signs or symptoms or radiological findings attributable to IFI while on treatment
Relapsed IFI	IFI occurring after antifungal treatment discontinuation. IFI is caused by the same pathogen at the same site with or without dissemination
Breakthrough IFI	IFI occurring during exposure to an antifungal drug, including fungi outside the spectrum of activity of an antifungal (treatment emergent IFI is a synonym); The time point of breakthrough IFI is the first attributable clinical sign or symptom, mycological findings or radiological feature; The period of breakthrough IFI depends on the pharmacokinetic properties of the antifungal evaluated

Tanım	Tanımlama
Persistent İFE	Başlangıçtan beri değişmeyen İFE, tedavi başarısından önce gelebilir
Refrakter İFE	Tedavi sırasında kötüleşen veya yeni atfedilebilir klinik belirtiler veya semptomlar veya IFE'ye atfedilebilen radyolojik bulgular
Relaps İFE	Antifungal tedavi kesildikten sonra ortaya çıkan IFI. IFE dissemine olarak/olmayarak aynı bölgedeki aynı patojenden kaynaklanıyor.
***"Breakthrough"* İFE**	• Bir antifungale maruz kalma sırasında gelişen İFE, • bir AF etki spektrumu dışında mantar dahil (treatment emergent IFI); • BİFE'nin tanı zaman noktası, İFE'ye ilk atfedilebilir klinik belirti veya semptom, mikolojik bulgular veya radyolojik özelliktir; • BİFE'nin periyodu, değerlendirilen antifungalin farmakokinetik özelliklerine bağlıdır.

Cornely OA et al. Mycoses. 2019;62:716–729.

Table 37

Antifungal drugs in refractory disease

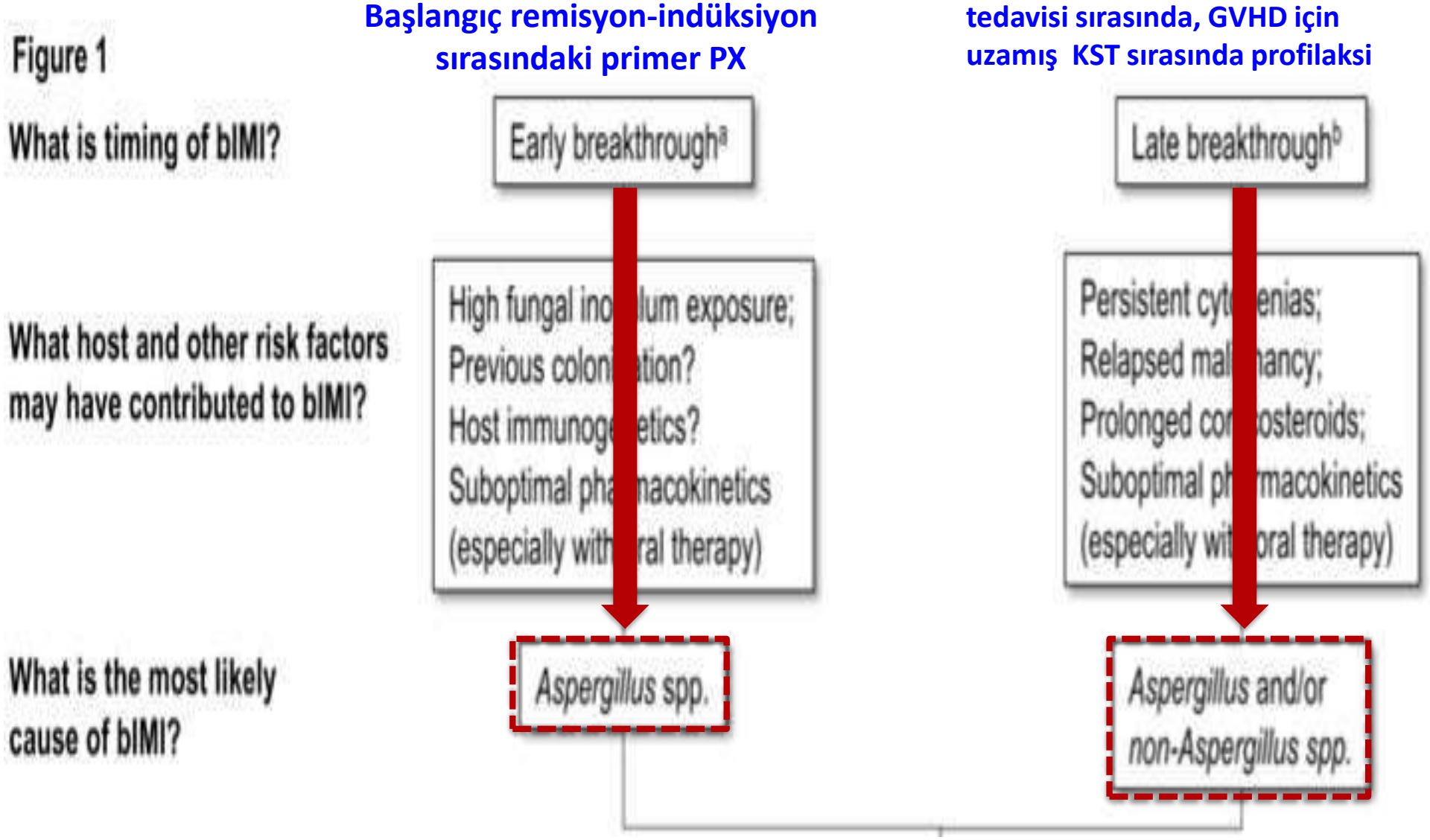
Population	Intention	Intervention	SoR	QoE	Comment
Haematological patients with refractory IA	Achieve complete or partial response, or stable disease, improve survival	Switch to another drug class	A	III	
		Any combination	C	III	No prospective study demonstrated superiority of combination therapy over monotherapy
		Voriconazole	A	II	
		L-AmB 3–5 mg/kg	B	II	Majority voted for BII others for AII
		ABLC 5 mg/kg	C	II	
		ABCD			No longer commercially available
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	B	II	Very few data in case of voriconazole/ posaconazole failure
		Micafungin 75–200 mg qd	C	II	
		Posaconazole 200 mg qid or 400 mg bid suspension or 300 mg tablet bid day 1, followed by 300 mg qd	B	II	
		Itraconazole	D	III	In case of refractoriness to voriconazole
		Itraconazole oral forms	C	II	Poor bioavailability
		Itraconazole IV formulation			Commercially not available everywhere

Tanım	Tanımlama
Persistent İFE	Başlangıçtan beri değişmeyen İFE, tedavi başarısından önce gelebilir
Refrakter İFE	Tedavi sırasında kötüleşen veya yeni atfedilebilir klinik belirtiler veya semptomlar veya IFE'ye atfedilebilen radyolojik bulgular
Relaps İFE	Antifungal tedavi kesildikten sonra ortaya çıkan IFI. IFE dissemine olarak/olmayarak aynı bölgedeki aynı patojenden kaynaklanıyor.
"Breakthrough"* İFE** ***Cornely OA et al. Mycoses. 2019;62:716–729.	• Bir antifungale maruz kalma sırasında gelişen İFE (PX, ampirik, preemtif) , • bir AF etki spektrumu dışında mantar dahil (treatment emergent IFI); • BİFE'nin tanı zaman noktası, İFE'ye ilk atfedilebilir klinik belirti veya semptom, mikolojik bulgular veya radyolojik özelliktir; • BİFE'nin periyodu, değerlendirilen antifungalin farmakokinetik özelliklerine bağlıdır.

Breakthrough İFE

Başlangıç remisyon-indüksiyon sırasındaki primer PX

Relaps lösemi için re-indüksiyon tedavisi sırasında, GVHD için uzamış KST sırasında profilaksi



Lionakis MS et al.Clinical Infectious Diseases, Volume 67, Issue 10, 2018, Pages 1621–1630,

What is the diagnostic work-up of bIMI?

CT of lung[c] +/-sinus[d] ± brain[d, #, ##]
Early bronchoscopy (within 48-72 hours)
Bronchoalveolar lavage fluid culture, galactomannan, PCR;[e]
Antifungal susceptibility testing of isolates grown from culture;[f]
Biopsy, histology and culture of suspected lesions if feasible

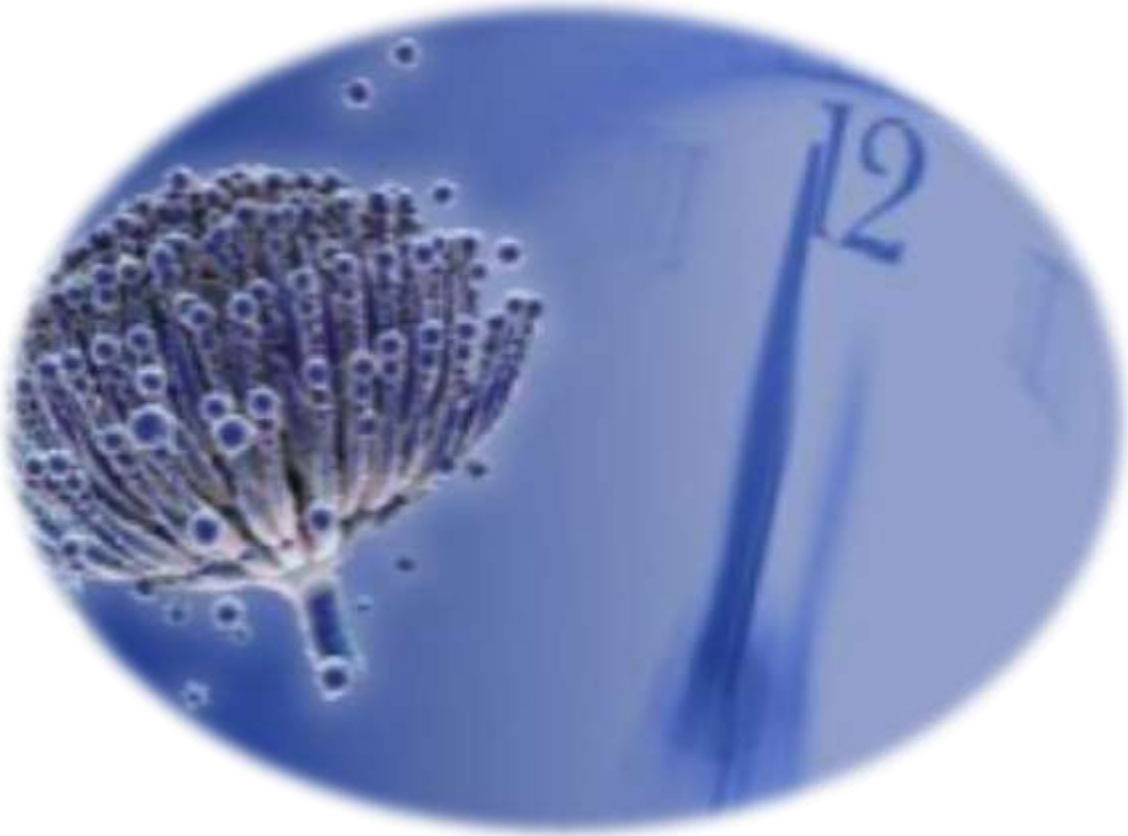
How does the antifungal at time of breakthrough affect work-up?

POS[#] or ISA[#]	VRC	Lipid AMB	Echinocandin[##]
TDM should be considered to document drug exposures, especially for patients on oral therapy Risk for breakthrough with non-*Aspergillus* molds or resistant *Aspergillus* spp.	TDM important to document drug exposures due to extreme PK variability Risk for breakthrough with non-*Aspergillus* spp. (especially mucormycosis) or resistant *Aspergillus* spp.	Increased concern for *A. terreus*, *A. flavus* and amphotericin B-resistant non-*Aspergillus* molds (e.g., *Cunninghamella*, *Scedosporium*, *Paecilomyces*)	Breakthrough infection with all *Aspergillus* spp. and non-*Aspergillus* molds

Initial treatment until more definitive diagnosis:

Switch to a different triazole* with similar spectrum (POS→ISA, or ISA→POS) + L- AMB (5 mg/kg/day)	Switch to a mold-active triazole* with broader spectrum (POS or ISA) + L-AMB (5 mg/kg/day)	Mold-active triazole* (VRC, ISA) +/- Echinocandin	Mold-active triazole* (VRC, ISA) +/- L-AMB (5mg/kg/day)

Lionakis MS et al.CIID, Volume 67, Issue 10, Pages 1621–1630, 2018



TEŞEKKÜRLER