KANSER TEDAVİSİNDE ANTİMİKROBİYAL PROFİLAKSİ

Dr. Hamdi AKAN
Ankara Tıp Fakültesi Hematoloji Bilim Dalı

KOÇ ÜNİVERSİTESİ TIP FAKÜLTESİ

KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

FEN FEBRİL NÖTROPENİ Derneği

- Pro.phy.lax.is |ˌprōfəˈlaksəs|
- *KÖKEN 19. yüzyıl: modern Latin* ***pro-*** *2 [önce] + Yunanca phulaxis 'koruma işi.'*
- Bir hastalığı önlemek için özel önlem alma

- Kimi
- Kime karşı?
- Ne zaman?
- Ne ile?
- Nasıl?


Antifungal
Antibakteriyel
Antiviral
Anti-PJP
Anti-TB

ANTİBAKTERİYEL PROFİLAKSİ

Questionnaire on European practices: Antibacterial Prophylaxis

38 respondants : 23 (61%) use antibacterial prophylaxis

Setting in which prophylaxis is used	
Allo HSCT	83%
AutoHSCT	61%
AL induction	69%

Time of Initiation	alloHSCT	autoHSCT	induct.
Before the onset of Neutropenia	78%	78%	87%

Duration of proph.	alloHSCT	autoHSCT	induct.
Until the end of of Neutropenia	79%	86%	87%

STOP at onset of fever ? YES	
Allo HSCT	68%
AutoHSCT	64%
AL induction	69%

Type of Regimen	alloHSCT	autoHSCT	induct.
QUINOLONES	**16/23 (70%)**	**12/16 (75%)**	**13/18 (72%)**
Ciprofloxacin	11/19 (58%)	8/14 (57%)	10/16 (62%)
Levofloxacin	3/19 (16%)	3/14 (21%)	2/16 (25%)
TMP/SFM	**1/23 (4%)**	**1/16 (6%)**	-

META-ANALYSES

Anat Gafter-Gvili et al.
Annals of Internal Medicine, 2005: 17 trials (1409 patients)

Van de Wetering et al.
European Journal of Cancer, 2005: : 8 trials (746 patients)

Engels et al.
Journal of Clinical Oncology, 1998 : 9 trials (731 patients))

CLINICAL TRIALS

Bucaneve and GIMEMA
New England Journal of Medicine, 2005 (760 patients)

Cullen et al.
New England Journal of Medicine, 2005 (1565 patients)

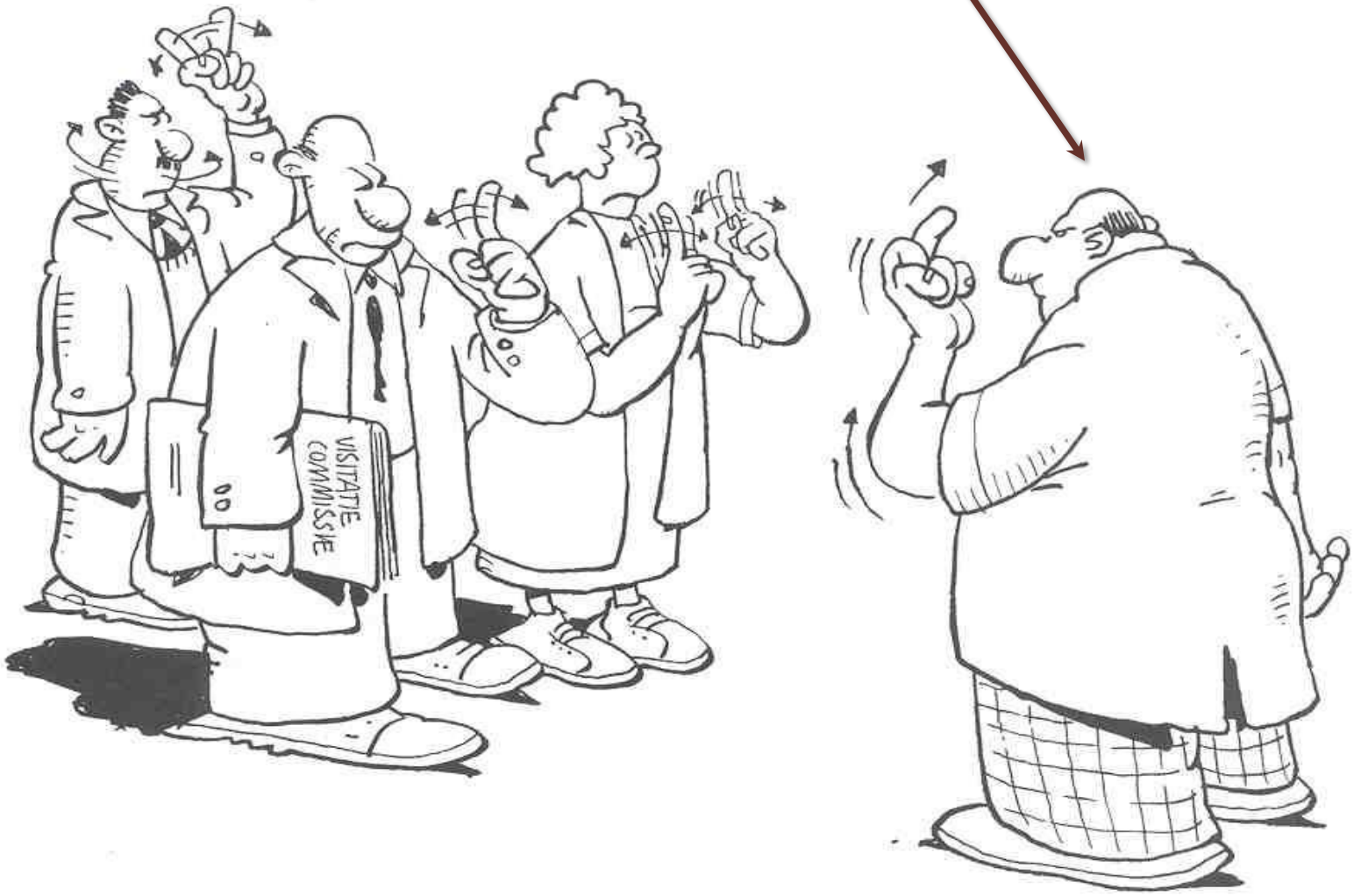
ECIL

Drug of Choice	Strength of Recommendation and level of evidence
Levofloxacin (500 mg once daily):	AI
Ciprofloxacin (500 mg bid):	AI
Ofloxacin (200 - 400 mg bid):	BI
Norfloxacin (400 mg bid):	BI

SÜREKLİ İZLEME:

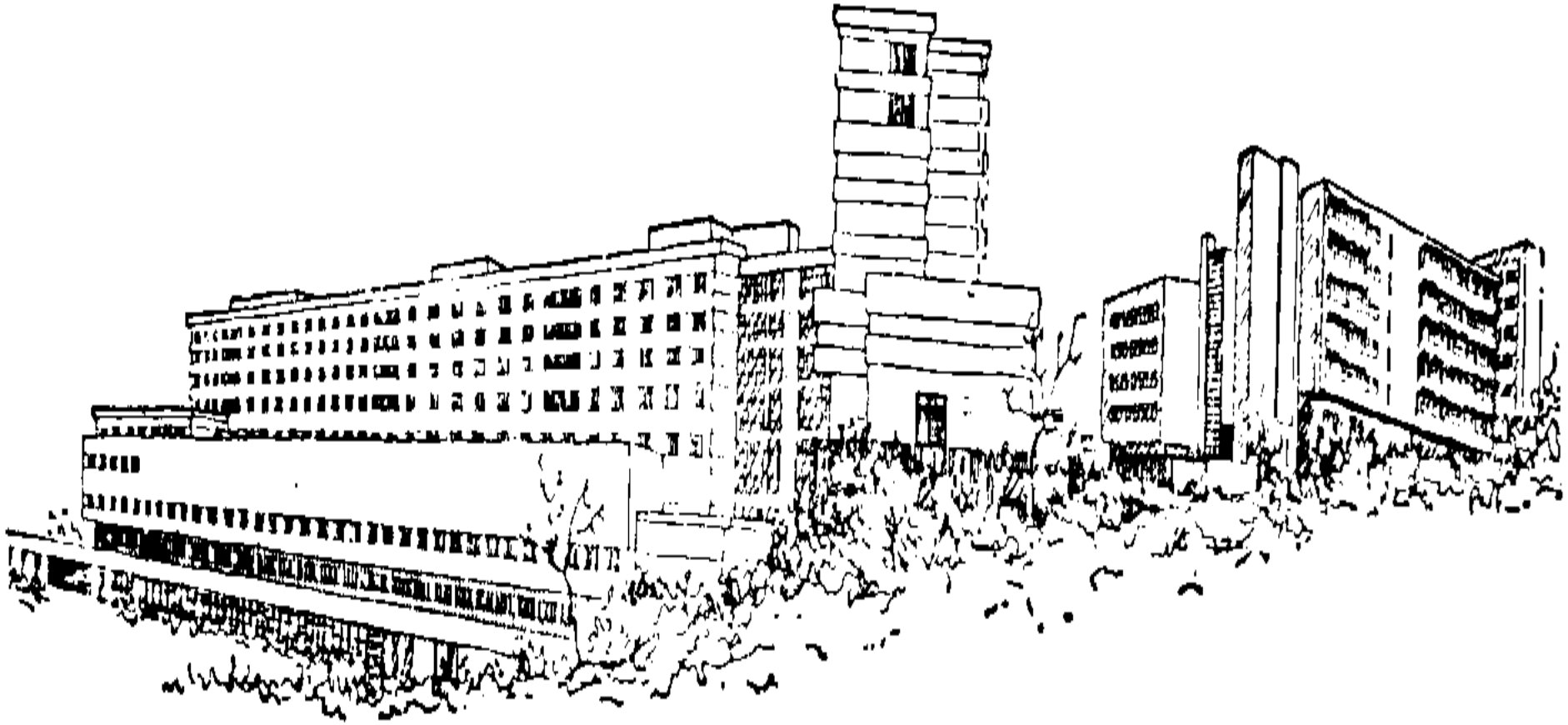
1. Ampirik antibakteriyel tedavide artış olursa
2. Gram negatiflerde florokinolon direnci artarsa
3. Mortalite'de artış olursa

Kılavuzlar mı, günlük pratik mi?



Ben de Pauw'dan alınma

Quinolone Prophylaxis: Think Twice Before Giving



Nötropenik hastada Kinolon profilaksisi

Olumlu:

- Gram-negatif bakteremi azalıyor
- Mortalite azalıyor

Olumsuz

- Q-R bakteri ile kolonizasyon artıyor
- Q-R bakteri ile infeksiyon artıyor

Gafter-Gvili A, et al. Ann Intern Med 2005;142:979

Leibovici L, et al Cancer 2006;107:1743

Gafter-Gvili, et al. JAC 2007;59:5

Mortalite ? Metaanalizlerde fark var…

Randomize çalışmalarda yarar yok..

Metanalizlerde kinolonlar yararlı:

- Akut lösemi
- Solid tümör

Bucaneve G, et al. 2005;353:977
Leibovici L, et al 2006;107:1743

Akut Lösemi ve AKHN alt analizleri

Profilaksi ile ölümde azalma var.

Çalışmalar çok heterojen:

- 18 yılda 10 çalışma
- 5 ayrı Kinolon
- 3 tanesi norfloxacin
- 1 tanesi cipro + co-amoksiklav..

Leibovici L, et al. Cancer 2006;107:1743
Hammond SP& Baden LR. Leukemia and Lymphoma 2008;49:183

Kinolon-R bakteri kolonizasyon ve infeksiyonu

- Metaanalizde profilaksi plasebodan farklı değil.

  Gafter-Gvili, et al. JAC 2007;59:5

- Veri az ya da yok:
  - Geldiğinde kolonizasyon
  - Kinolonların direnç gelişimi üzerine etkisi

Table 1. Antibacterial consumption in Turkey between 2001 and 2006

	DDD/1000 inhabitant-days					
Antibacterial class	2001	2002	2003	2004	2005	2006
Tetracyclines (J01)	0.850	0.911	0.929	0.917	1.261	1.203
Amphenicols (J01B)	0.015	0.012	0.011	0.009	0.010	0.008
Penicillins (J01C)	7.126	7.666	8.115	9.734	14.043	14.087
Cephalosporins (J01DA)	1.984	2.402	2.510	3.223	5.640	6.213
Carbapenems (J01DH)	0.003	0.003	0.003	0.003	0.006	0.007
Macrolides and lincosamides (J01F)	2.833	2.587	2.914	3.446	5.848	5.515
Aminoglycosides (J01G)	0.176	0.155	0.155	0.138	0.171	0.157
Quinolones (J01M)	1.543	1.682	1.809	2.173	3.409	3.823
Glycopeptides (J01XA)	0.003	0.003	0.003	0.003	0.006	0.007
Antibacterials for systemic use (total) (J01)	14.620	15.500	16.530	19.740	30.560	31.360

Karabay O and Hosoglu S. J Antimicrob Chemother 2008;61:1169

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2009, p. 1287–1289 Vol. 53, No. 3
0066-4804/09/$08.00+0 doi:10.1128/AAC.01228-08

Prevalence and Risk Factors for Selection of Quinolone-Resistant *Escherichia coli* Strains in Fecal Flora of Patients Receiving Quinolone Therapy▽

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Ankara University, School of Medicine, Department of Clinical Microbiology and Infectious Diseases, Ankara, Turkey

Received 16 September 2008/Returned for modification 29 October 2008/Accepted 1 December 2008

Patients taking quinolones as inpatients ($n = 55$) or outpatients ($n = 40$) and newly hospitalized patients who were not on quinolone therapy ($n = 41$) were assessed for fecal carriage of quinolone-resistant *Escherichia coli* (QREC) strains before and after therapy/hospitalization. Fluoroquinolone use in the previous 6 months was found to be a risk factor for QREC carriage before therapy/hospitalization. The prevalence of QREC strains in fecal flora increased steadily with the duration of quinolone therapy.

Quinolones, with their enhanced systemic activity against many gram-negative aerobes, have been widely used since the first introduction of ciprofloxacin in 1987 (3). It was suggested that the rapid bactericidal activity of quinolones would be advantageous for minimizing resistance. However, as the use

age, sex, underlying disease, and receipt of quinolone or other antimicrobials or hospitalization in the previous 6 months were collected. Written informed consent was obtained from all patients.

We collected fecal samples from all patients at day zero, as

Kollateral Hasar
C. difficile

- İmmunosuprese hastada belirgin artış:
  - 0.34/1000 yatış (2000)'dan 4.05/1000 (2008) ($p<0.01$)

    Guidol C, et al. ECCMID 2009; abst:O153

- Hypervirülan C. difficile epidemisi (Quebec)
  - En önemli risk faktörü Kinolon kullanımı ⇦

    Pepin J, et al. CID 2005;41:1254

- Moxifloksasin>levofloksasin
  - %4 vs %21

    Von Baum H, et al. JAC 2006;58:891

Empirical Treatment of Community-Acquired Pneumonia and the Development of Fluoroquinolone-Resistant Tuberculosis

Richard Long,[1] Huey Chong,[3] Vernon Hoeppner,[5] Hareishun Shanmuganathan,[6] Kinga Kowalewska-Grochowska,[4] Cary Shandro,[4] Jure Manfreda,[7] Ambikaipakan Senthilselvan,[2] Abeer Elzainy,[1] and Thomas Marrie[1]

Departments of [1]Medicine and [2]Public Health Sciences, University of Alberta, [3]Capital Health Region, and [4]Provincial Laboratory for Public Health, Edmonton, Alberta, [5]Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, and Departments of [6]Medicine and [7]Medicine and Community Health Sciences, University of Manitoba, Winnipeg, Manitoba

(See the editorial commentary by Low on pages 1361–3)

Background. Fluoroquinolone (FLQ) antibiotics are not uncommonly prescribed for community-acquired pneumonia that is later proven to be pulmonary tuberculosis (TB). Such FLQ monotherapy may result in FLQ-resistant pulmonary TB.

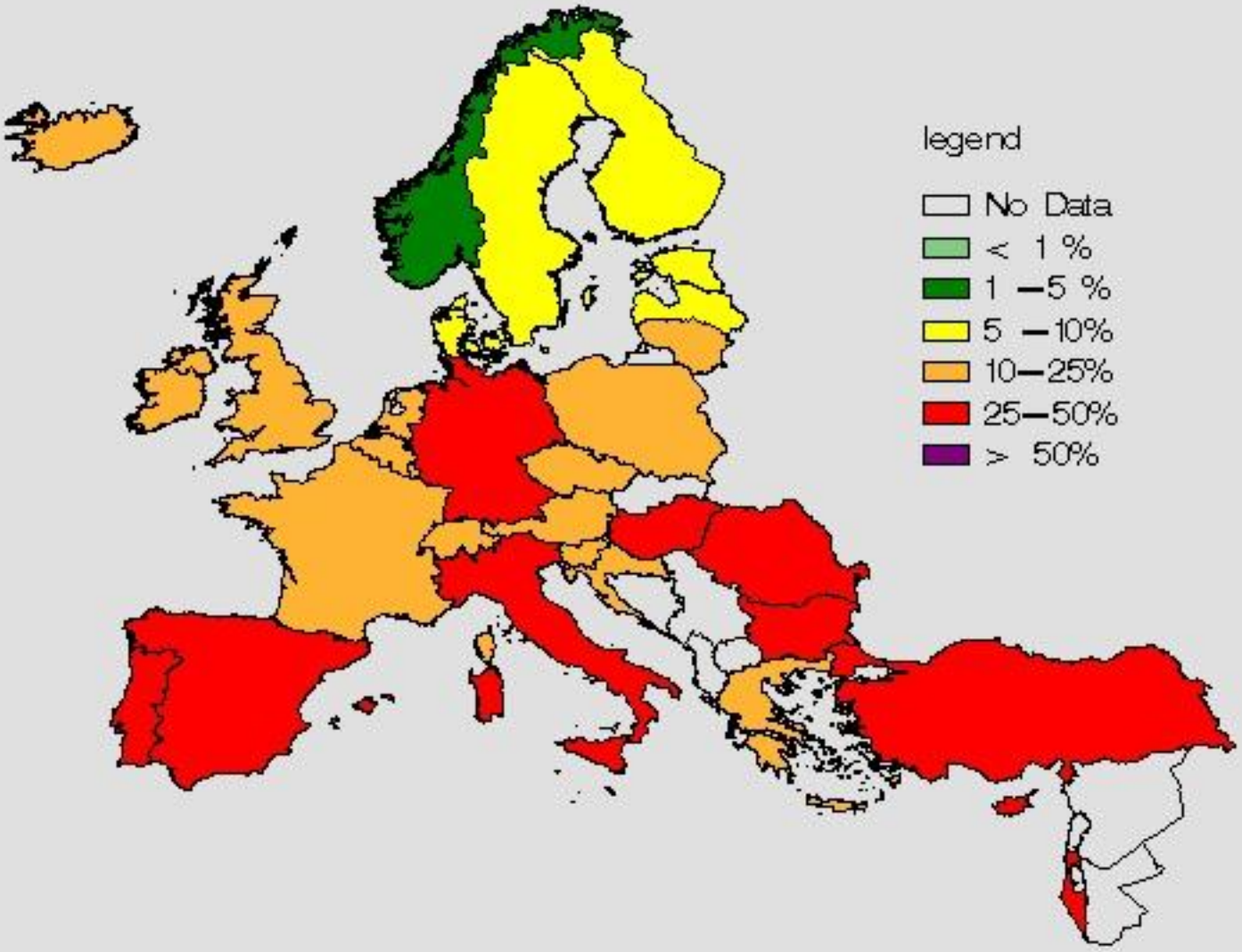
Methods. To assess outpatient FLQ use by patients with culture-proven pulmonary TB before diagnosis, TB registries in Alberta and Saskatchewan, Canada, were linked with provincial and federal drug benefit plans. To assess FLQ resistance, a case-control study was performed.

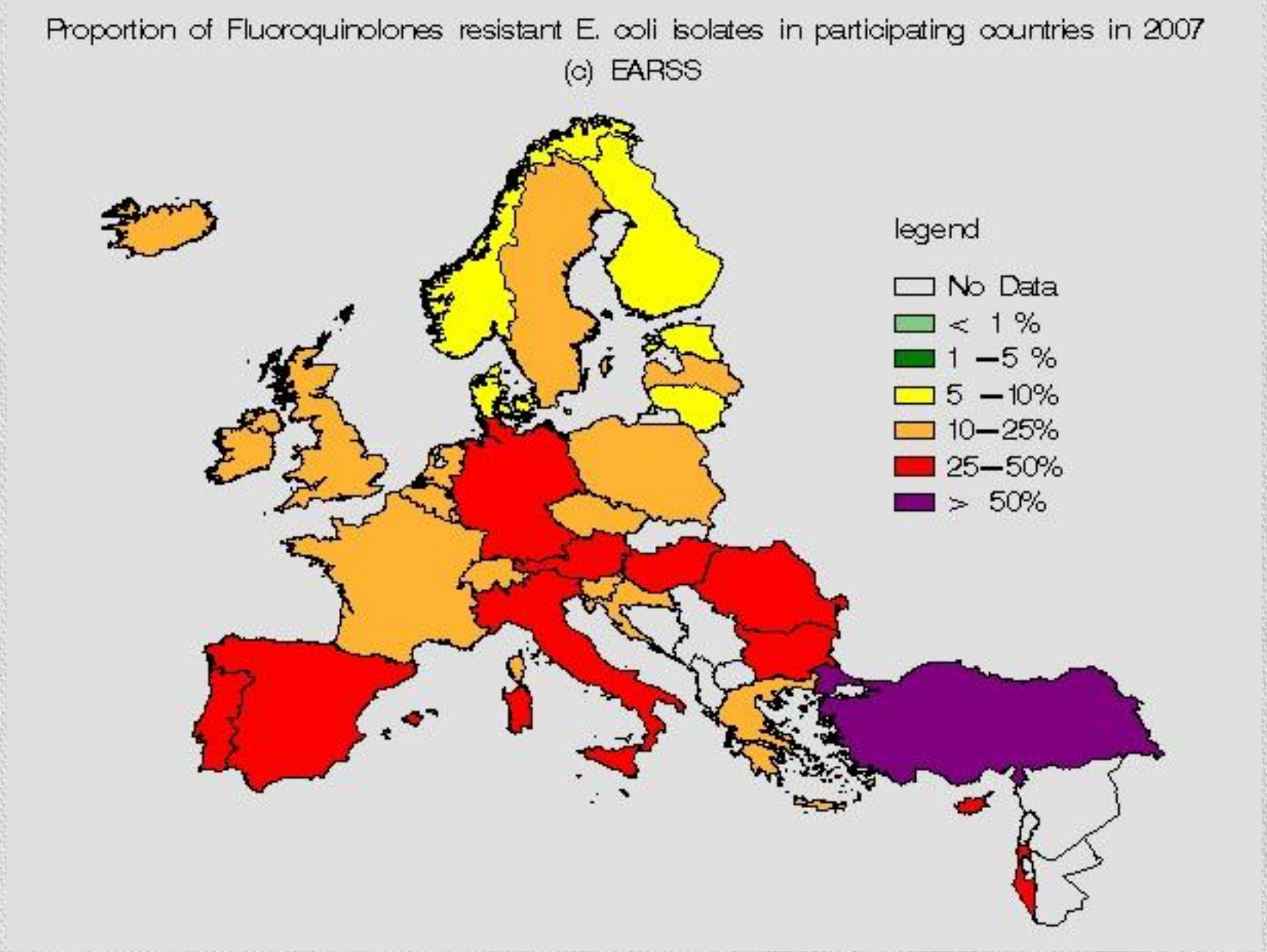
Results. Of 428 patients with pulmonary TB who were covered by a drug benefit plan, 74 (17.3%) had received ⩾1 FLQ prescription during the 6 months immediately before receipt of the diagnosis. Older patients (age, >64 years) were more likely than younger patients (age, 15–64 years) to be prescribed an FLQ ($P < .05$). Patients who were prescribed an FLQ received a total of 103 prescriptions. Most (54 [73.0%] of 74) patients who were prescribed an FLQ received a single prescription. Most (69 [67.0%] of 103) FLQ prescriptions were written within 90 days

Clin Infect Dis 2009; 15 May, 48:1354-60

Proportion of Fluoroquinolones resistant E. coli isolates in participating countries in 2006

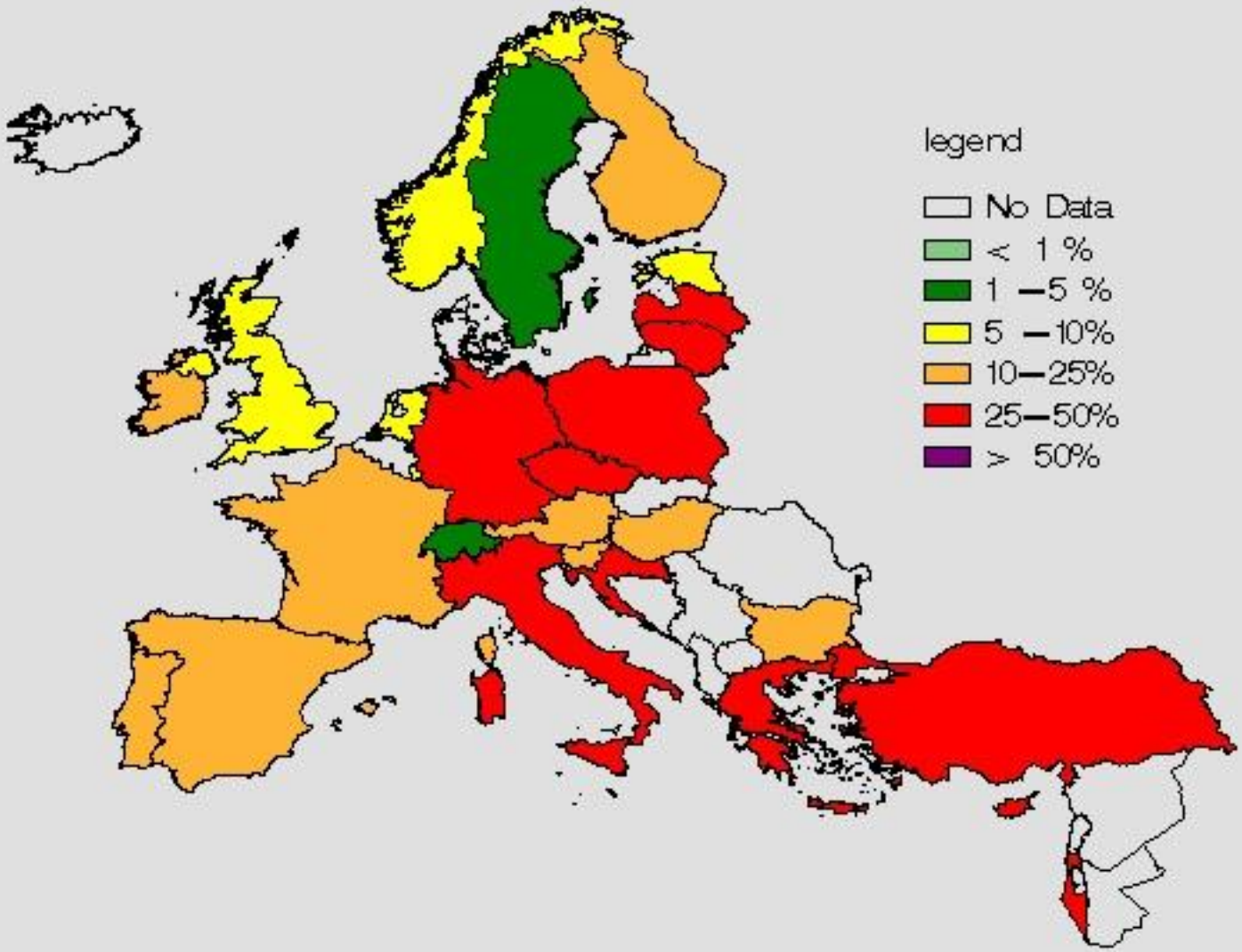
(c) EARSS




Proportion of Fluoroquinolones resistant E. coli isolates in participating countries in 2007
(c) EARSS
legend
No Data
< 1 %
1 –5 %
5 –10%
10–25%
25–50%
> 50%

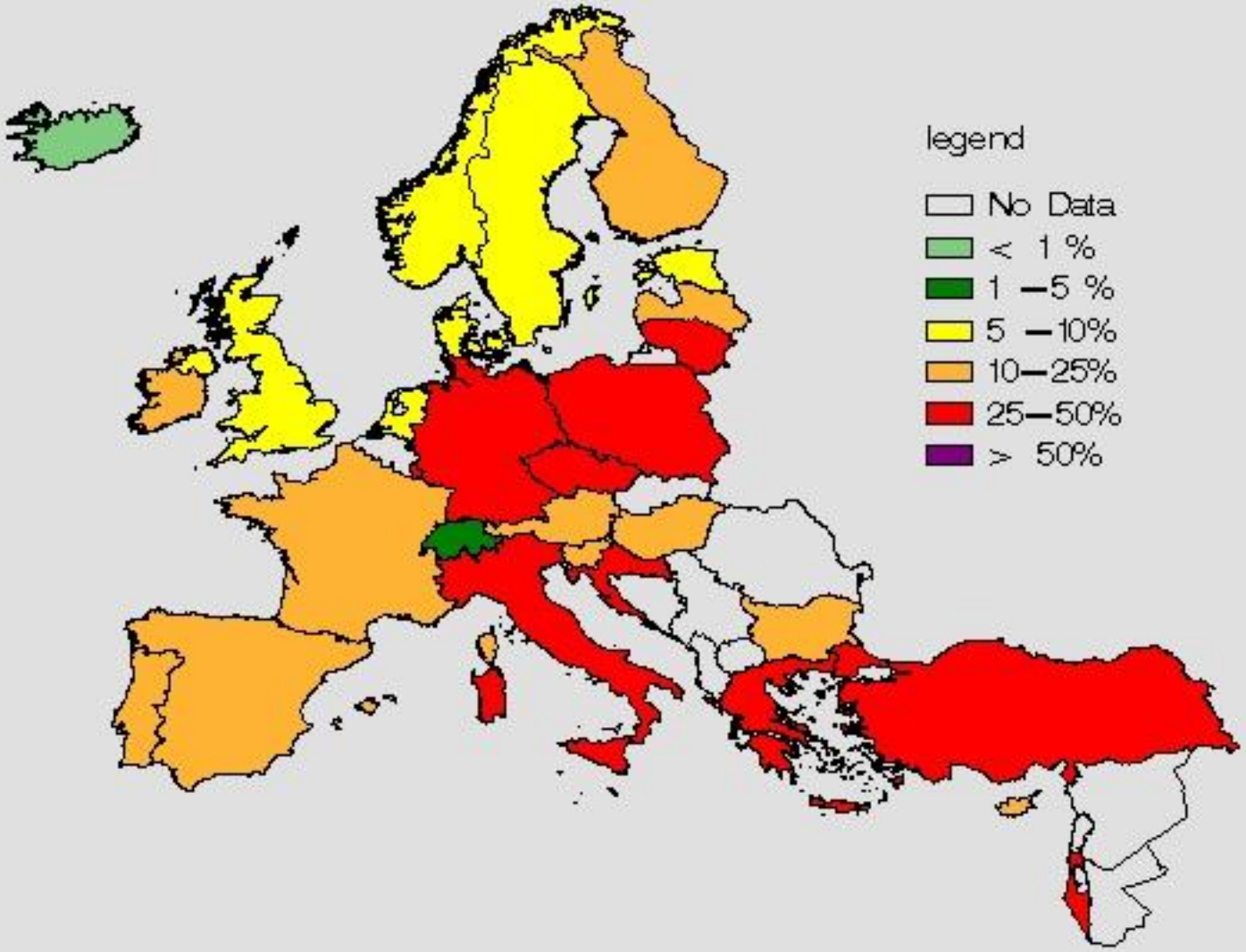
Proportion of Fluoroquinolones resistant P. aeruginosa isolates in participating countries in 2006

(c) EARSS

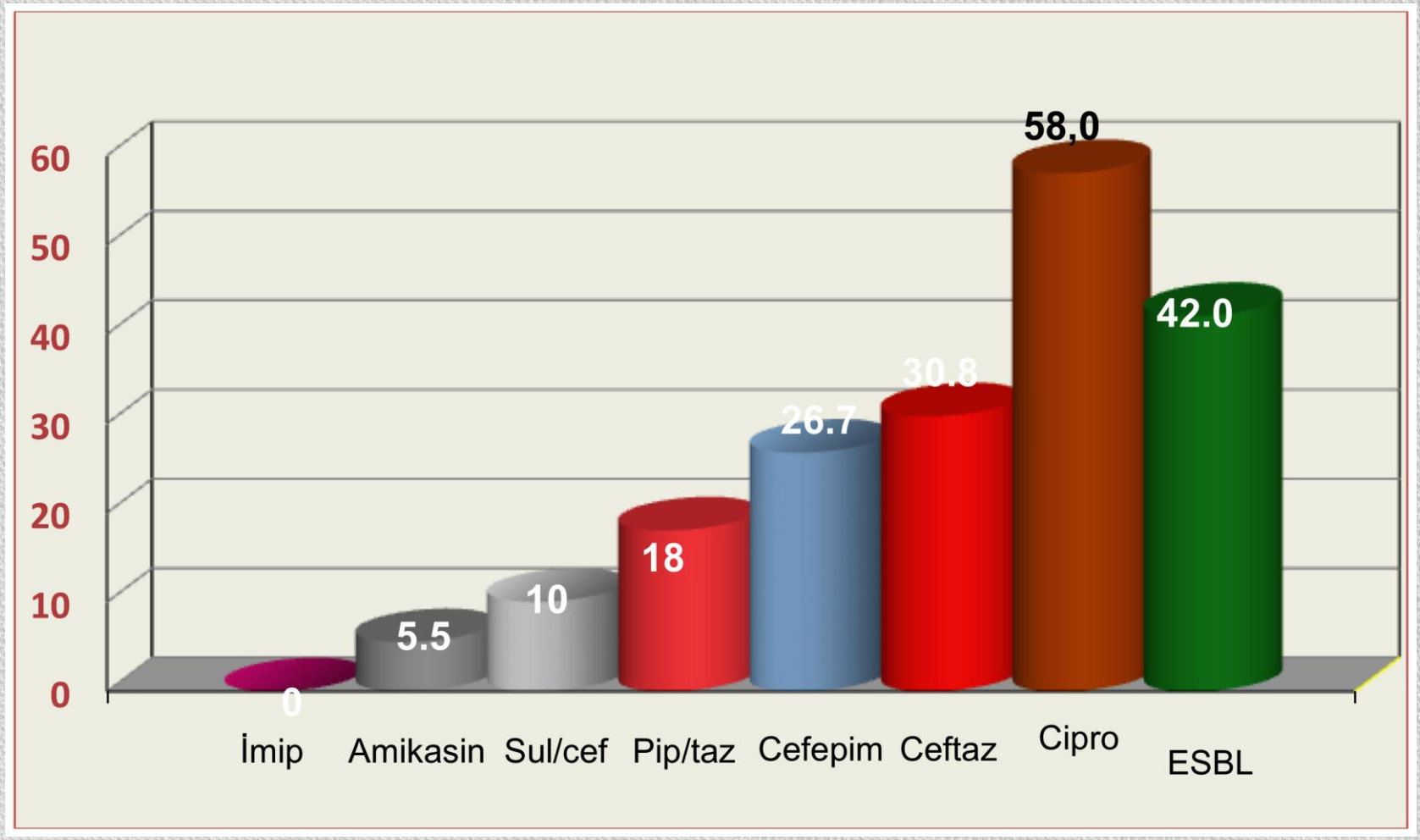


Proportion of Fluoroquindlones resistant P. aeruginosa isolates in participating ocuntries in 2007

(c) EARSS

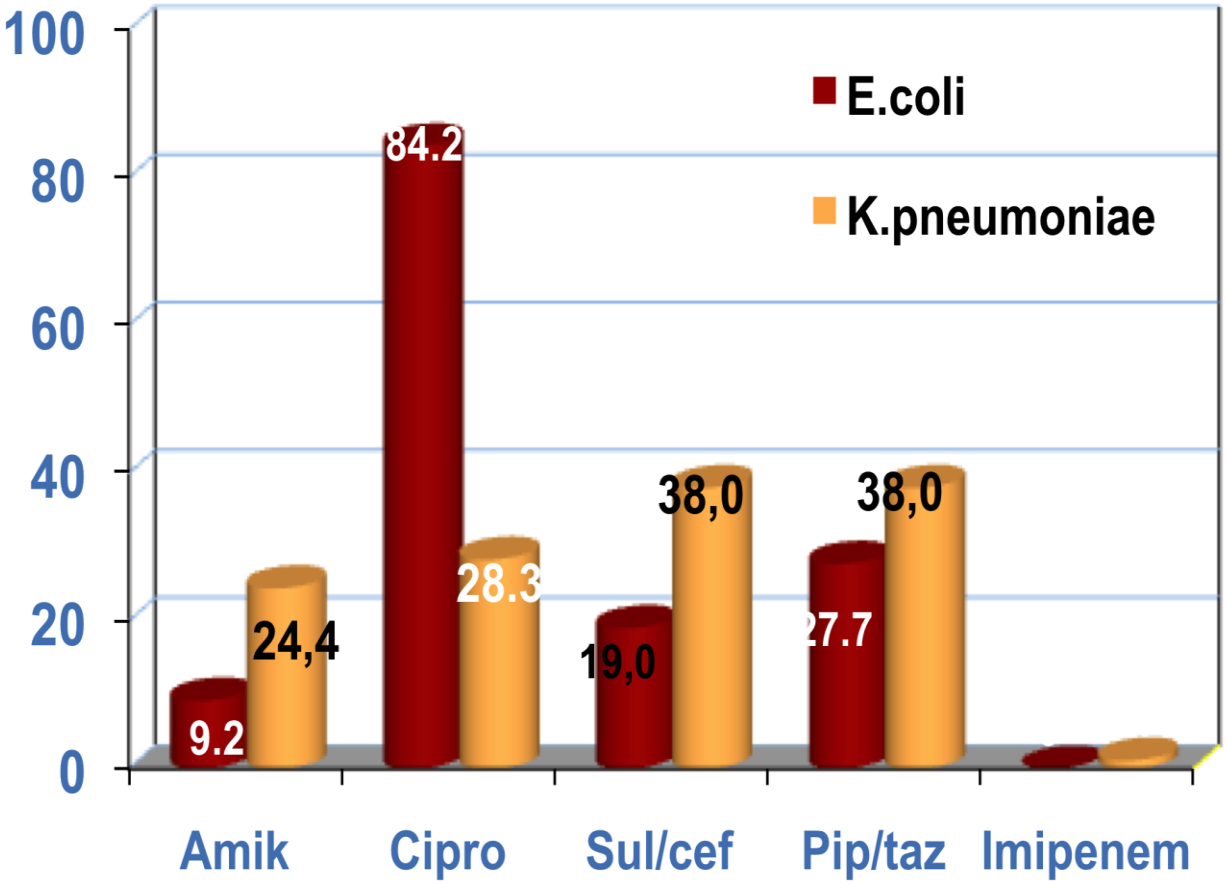


# *E.coli Direnci (%)*
n= 438



13 Türk Merkezi

ESBL (+) Izolatlar (%)

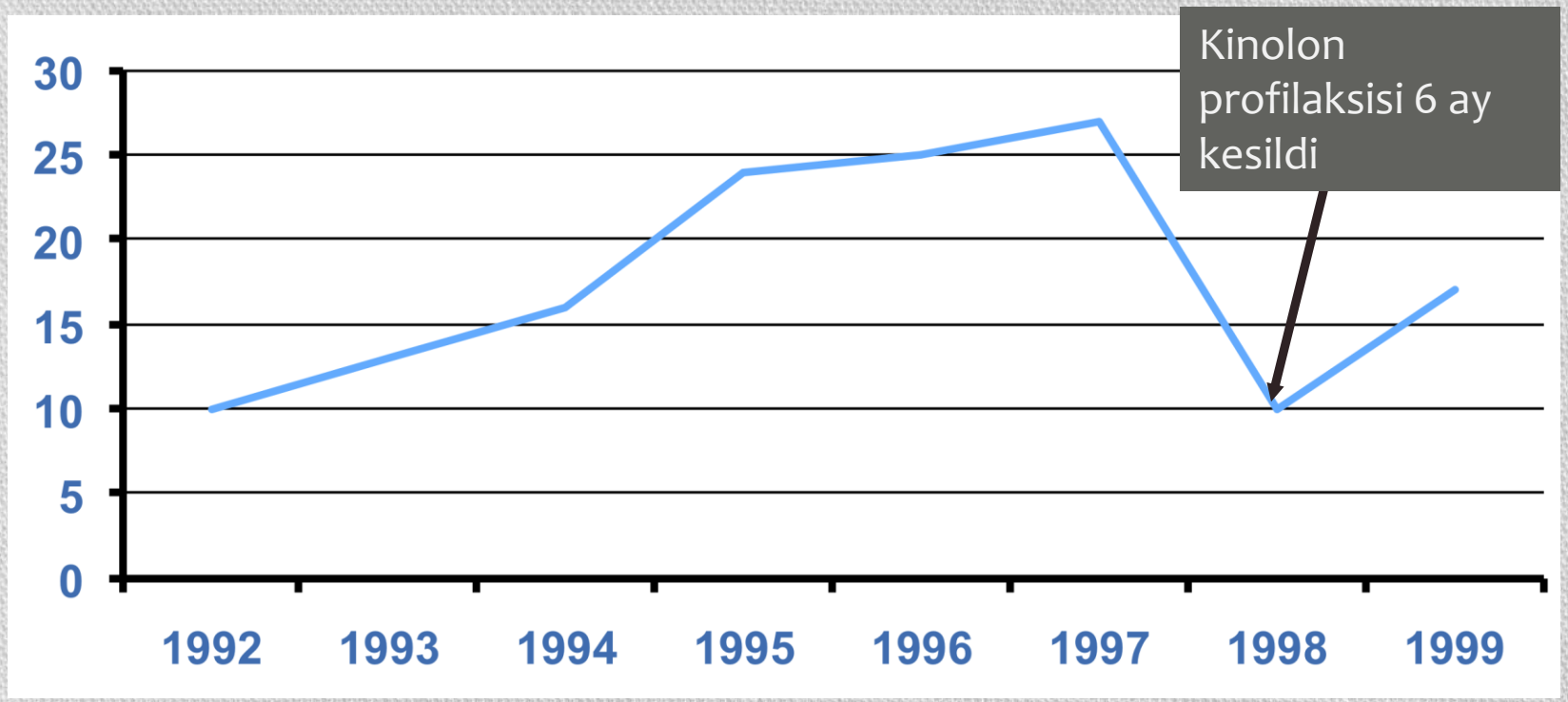


E. coli'de ESBL yapımı ve Kinolon direnci

- Tek merkez, retrospektif çalışma
- 62 Q-R *E. coli* bakteremili kanser hastası
- ESBL varsa mortalite belirgin derecede etkileniyor.

Trecarichi EM, et al. J Infect 2009;58:299

Hematoloji-Onkoloji olgularında Kinolon Dirençli *E. coli* Bakteremisi



Kern, et al. Eur J Clin Microbiol Infect Dis 2005;24:111

Profilaksi ile Gram (-) bakteremi azalıyor

- %9 vs %2 (p=0.01)
- 2007 Kasım'a kadar…

- Kinolon dirençli *E. coli* artışı ile gidiyor.

Kern VW, et al. ECCMID 2009; abst:O299

Sonuç

- Kinolon direnci önemli bir sorun
  - Diğer antimikrobiyallere de direnç artabilir
- Kinolon profilaksisi direnç arttıkça etkisiz oluyor
- Yarar kısa süreli

GUIDELINE ARTICLE

European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

Diana Averbuch,[1] Christina Orasch,[2] Catherine Cordonnier,[3] David M. Livermore,[4] Małgorzata Mikulska,[5] Claudio Viscoli,[5] Inge C. Gyssens,[6,7,8] Winfried V. Kern,[9] Galina Klyasova,[10] Oscar Marchetti,[2] Dan Engelhard,[1] and Murat Akova;[11] on

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Université Paris Est -Créte
University of Genova, IRC
and Immunity (N4i), Radb
and Infectious Diseases,
for Infectious Diseases an
[10]National Research Cente
University School of Medi

GUIDELINE ARTICLE

Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011)

Diana Averbuch,[1] Catherine Cordonnier,[2] David M. Livermore,[3] Małgorzata Mikulska,[4] Christina Orasch,[5] Claudio Viscoli,[4] Inge C. Gyssens,[6,7,8] Winfried V. Kern,[9] Galina Klyasova,[10] Oscar Marchetti,[5] Dan Engelhard,[1] and Murat Akova[11] on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

[1]Pediatric Infectious Diseases Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel; [2]APHP-Henri Mondor Hospital,
ch. UK,
epartment
mmation
icrobiology
m; [9]Center
rg, Germany;
, Hacettepe

The role of antibiotic stewardship in limiting antibacterial resistance among hematology patients

Inge C. Gyssens,[1,2,3] Winfried V. Kern,[4] and David M. Livermore;[5] on behalf of ECIL-4, a joint venture of EBMT, EORTC, ICHS and ESGICH of ESCMID

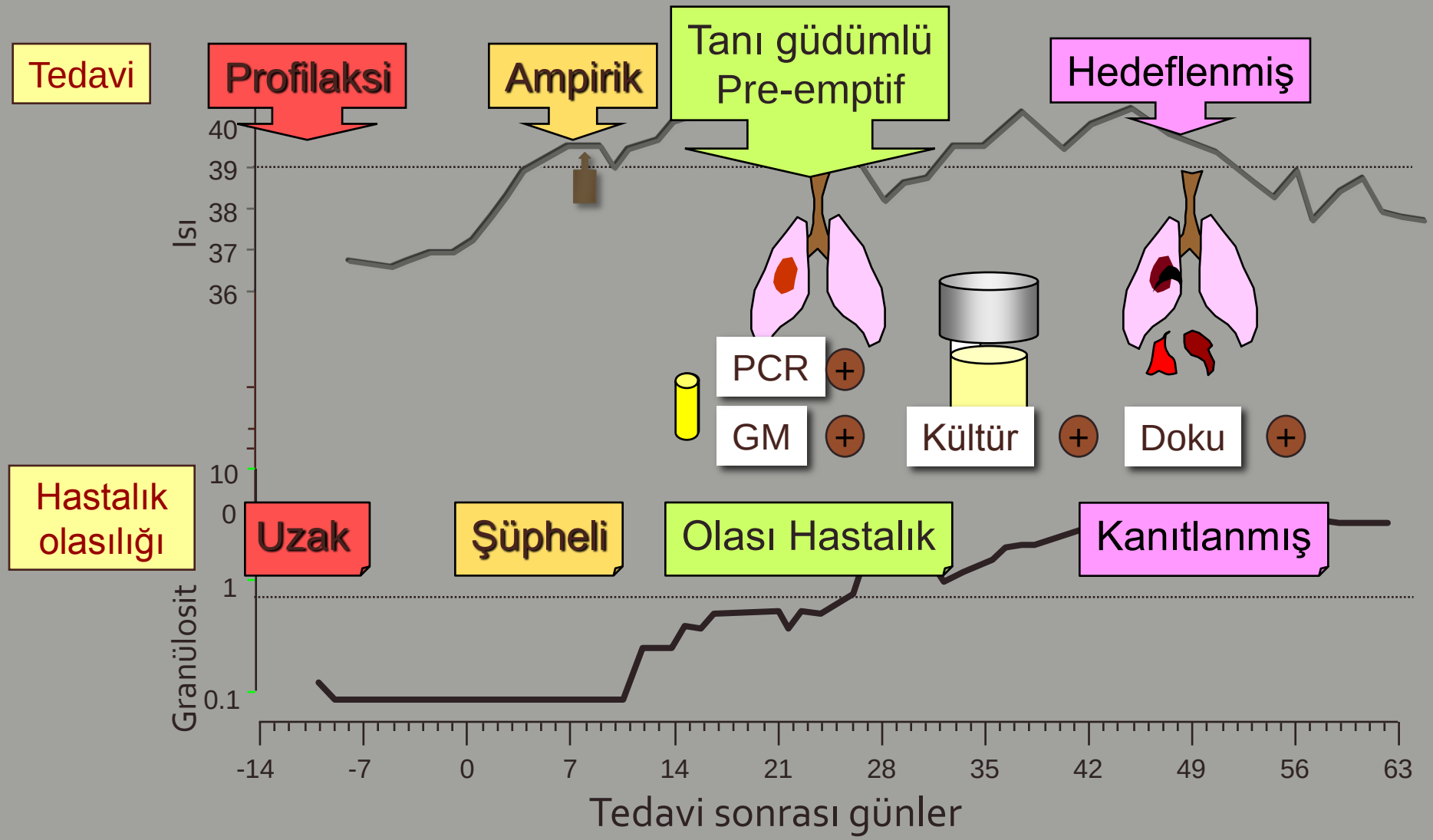
[1]Department of Medicine and Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; [3]Hasselt University, Hasselt, Belgium; [4]Center for Infectious Diseases and Travel Medicine, Department of Medicine, University Hospital, Freiburg, Germany; and [5]Norwich Medical School, University of East Anglia, Norwich, UK

E-mail: i.gyssens@aig.umcn.nl *doi:10.3324/haematol.2013.091769*

ANTİFUNGAL PROFİLAKSİ

- Neye karşı
- Kime
- Ne zaman
- Neyle
- Nasıl

YAKLAŞIMLAR



FUNGAL İNFEKSİYONLAR NİYE ARTIYOR?

Daha agresif anti-tümör tedaviler

Yoğun bakım ünitelerinde tedavi olan hastalar artıyor

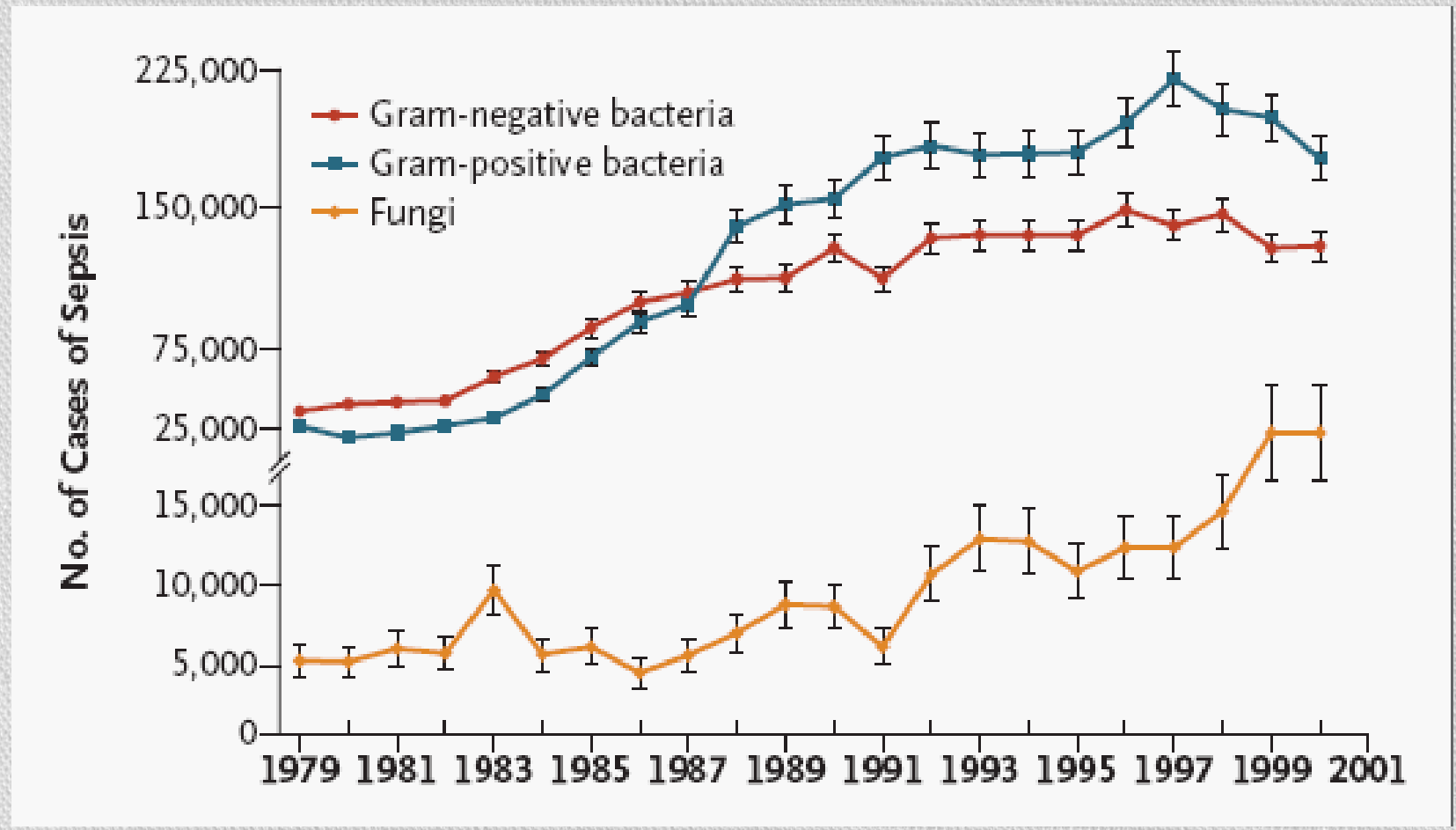
Daha çok,

- santral venöz kateter
- geniş spektrumlu antibiyotik kullanımı

Farkındalığın artması

Tanıda gelişmeler

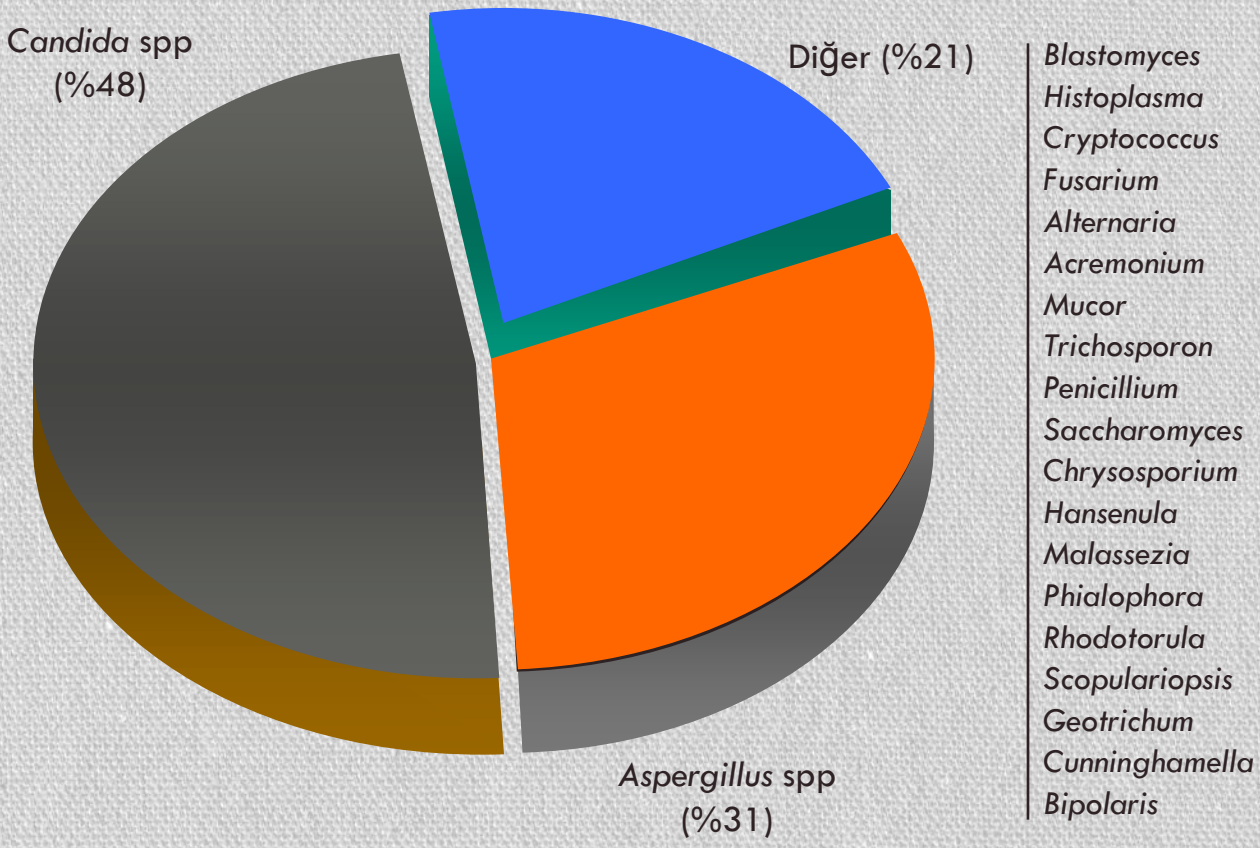
ABD'de sepsis epidemiyolojisi 1979-2000



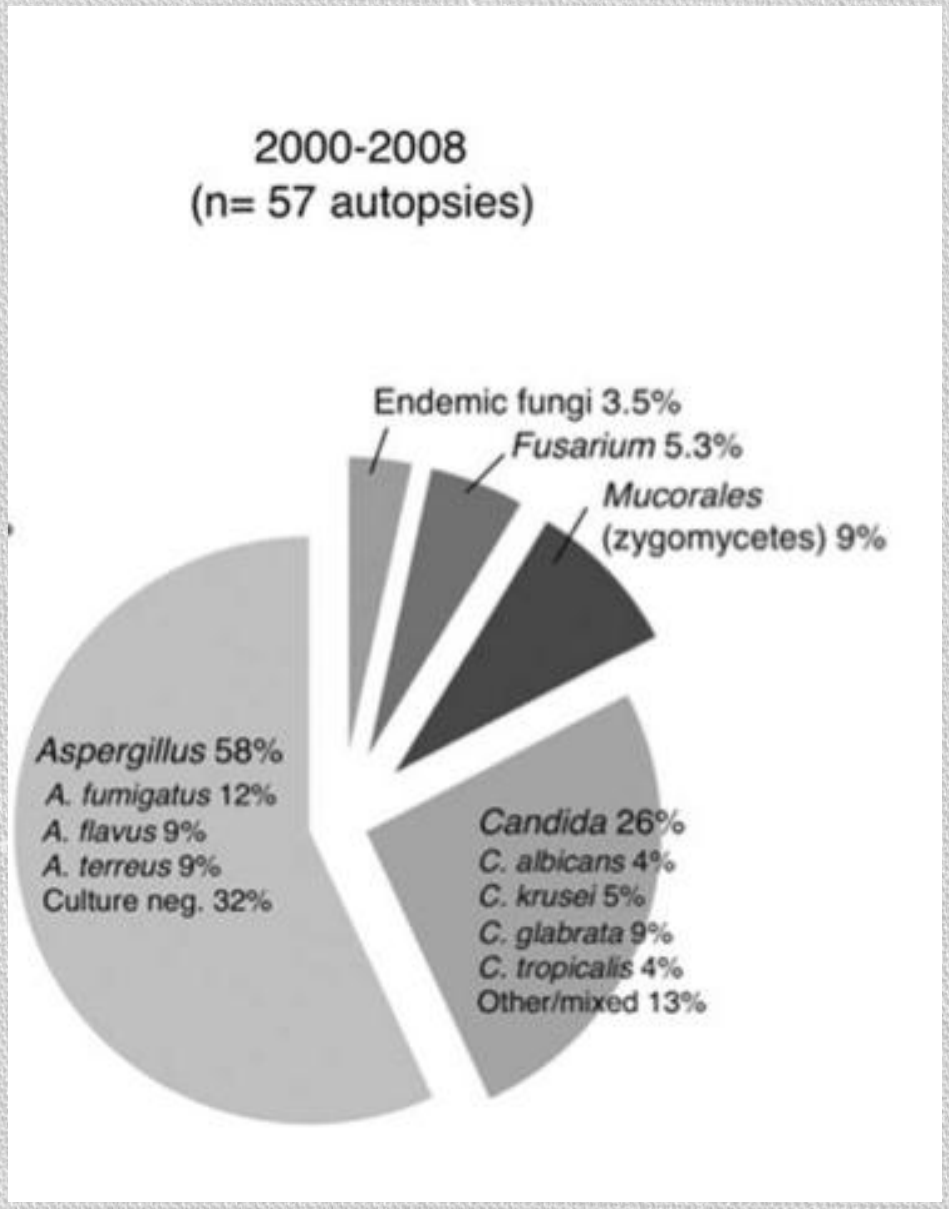
Martin GS, et al. N Engl J Med 2003;348:1546

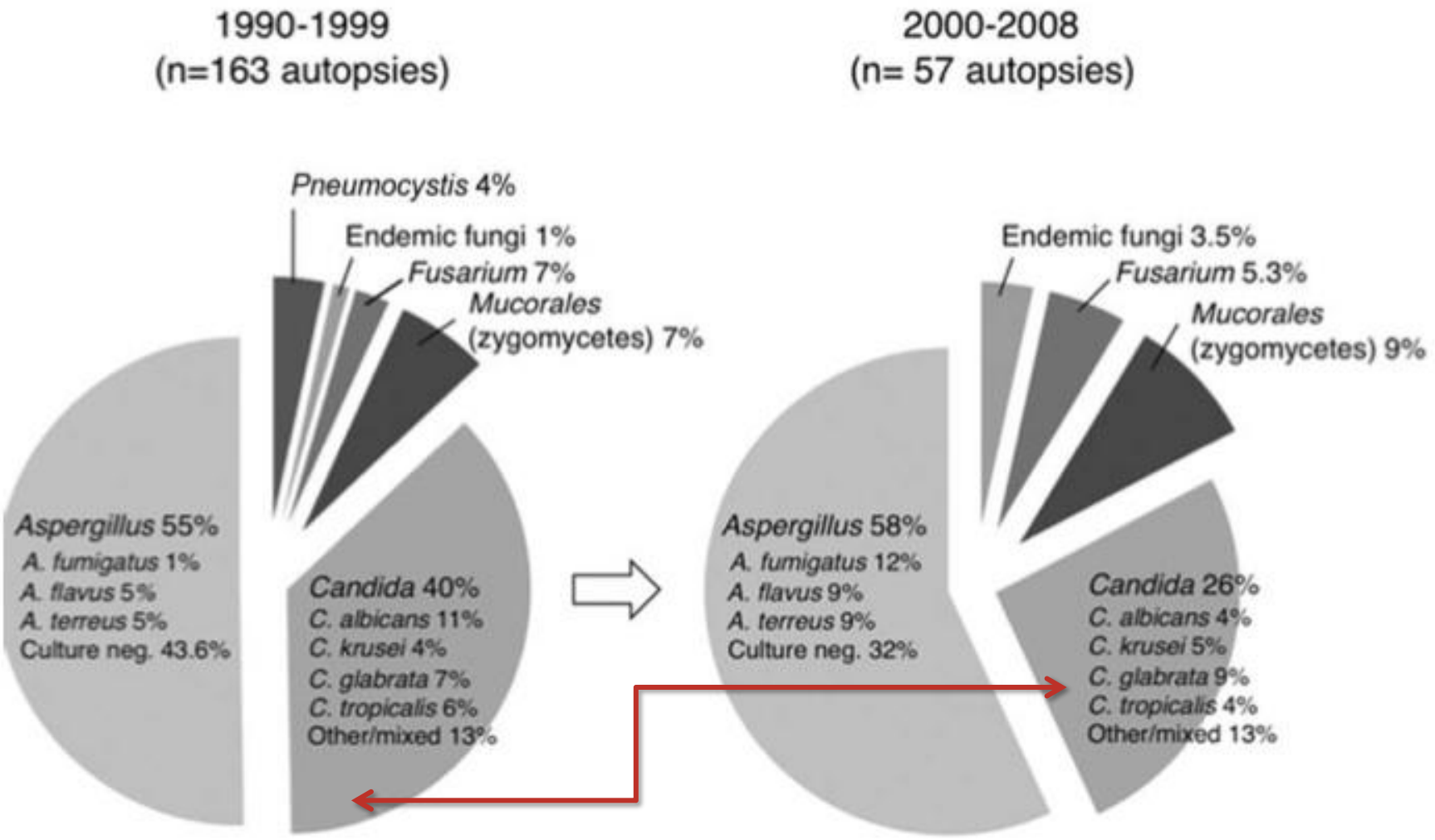
NEYE KARŞI?

Kanser Hastalarında Fungal İnfeksiyonlar



Walsh et al. Rev Infect Dis. 1991; Bodey et al. Eur J Clin Microbiol Infect Dis. 1992; Meunier et al. Clin Infect Dis. 1992; Vazquez et al. J Infect Dis. 1993; Pannuti et al. Cancer. 1992; Anaissie. Clin Infect Dis. 1992. Anaissie et al. Rev Infect Dis. 1989; Morrison et al. Am J Med. 1994.


2000-2008
(n= 57 autopsies)
Endemic fungi 3.5%
Fusarium 5.3%
Mucorales
(zygomycetes) 9%
Aspergillus 58%
A. fumigatus 12%
A. flavus 9%
A. terreus 9%
Culture neg. 32%
Candida 26%
C. albicans 4%
C. krusei 5%
C. glabrata 9%
C. tropicalis 4%
Other/mixed 13%


1990-1999
(n=163 autopsies)
2000-2008
(n= 57 autopsies)
Pneumocystis 4%
Endemic fungi 1%
Fusarium 7%
Mucorales
(zygomycetes) 7%
Aspergillus 55%
A. fumigatus 1%
A. flavus 5%
A. terreus 5%
Culture neg. 43.6%
Candida 40%
C. albicans 11%
C. krusei 4%
C. glabrata 7%
C. tropicalis 6%
Other/mixed 13%
Endemic fungi 3.5%
Fusarium 5.3%
Mucorales
(zygomycetes) 9%
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A. terreus 9%
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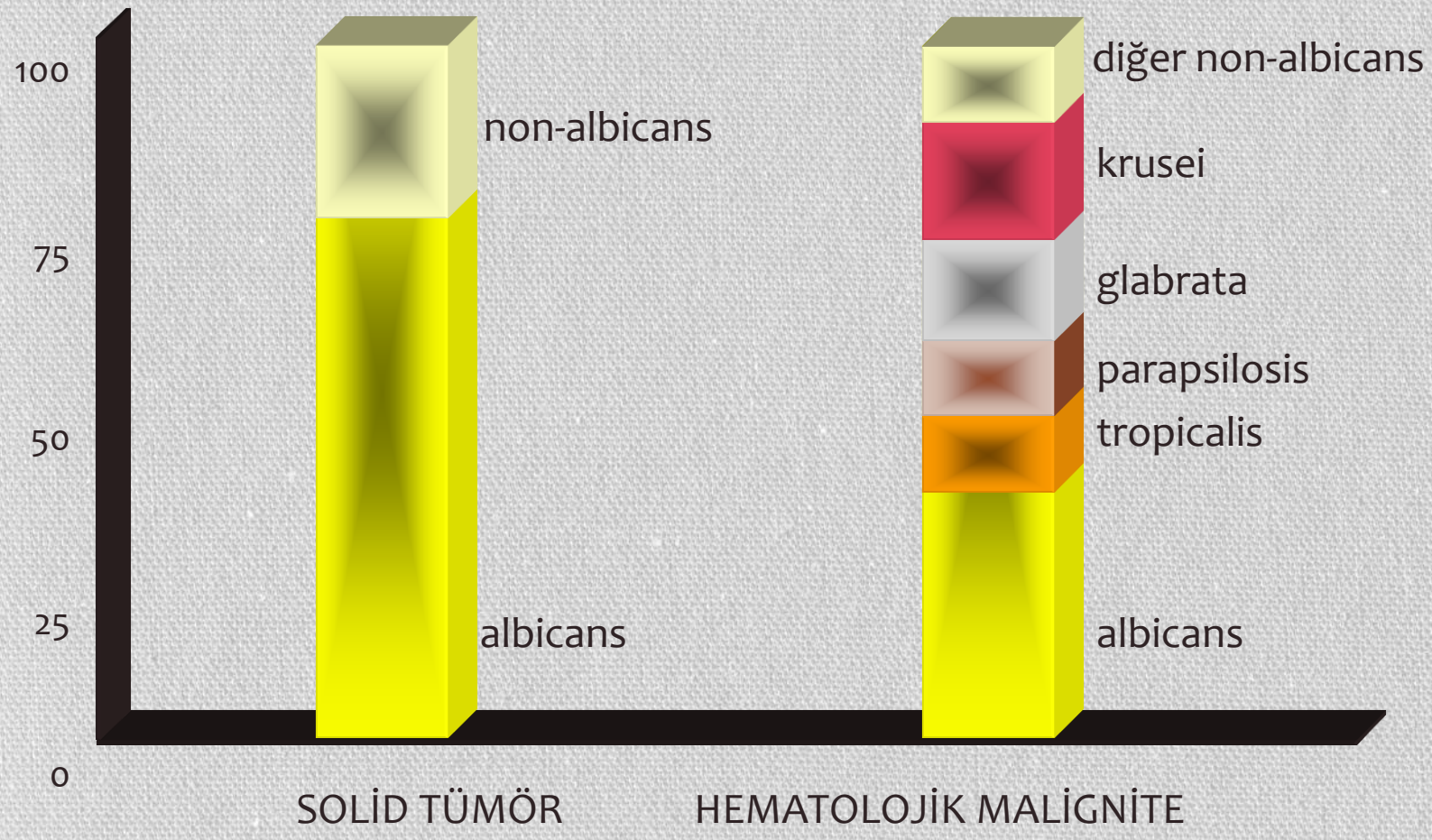
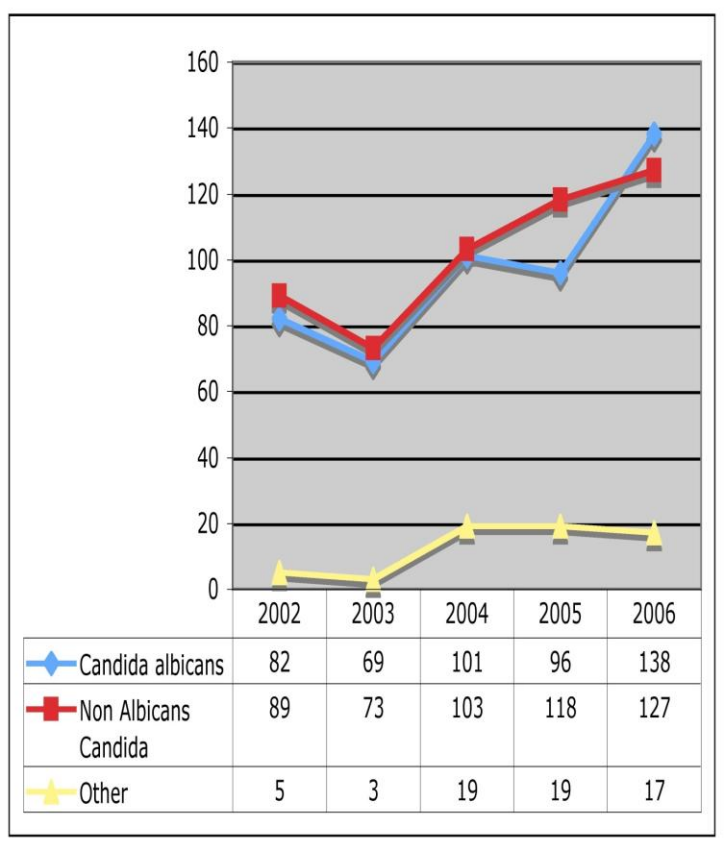
C. glabrata 9%
C. tropicalis 4%
Other/mixed 13%

NÖTROPENİ SIRASINDA KANDİDEMİ
EORTC 1996
ALTTA YATAN HASTALIĞIN ÖNEMİ

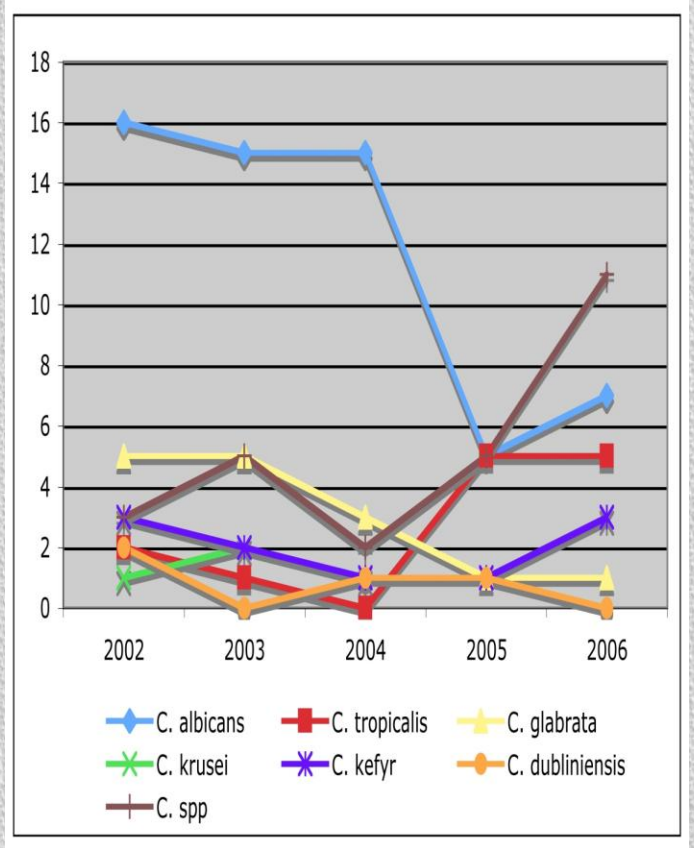


Ankara Tıp Fakültesinde Candidemi



	2002	2003	2004	2005	2006
Candida albicans	82	69	101	96	138
Non Albicans Candida	89	73	103	118	127
Other	5	3	19	19	17

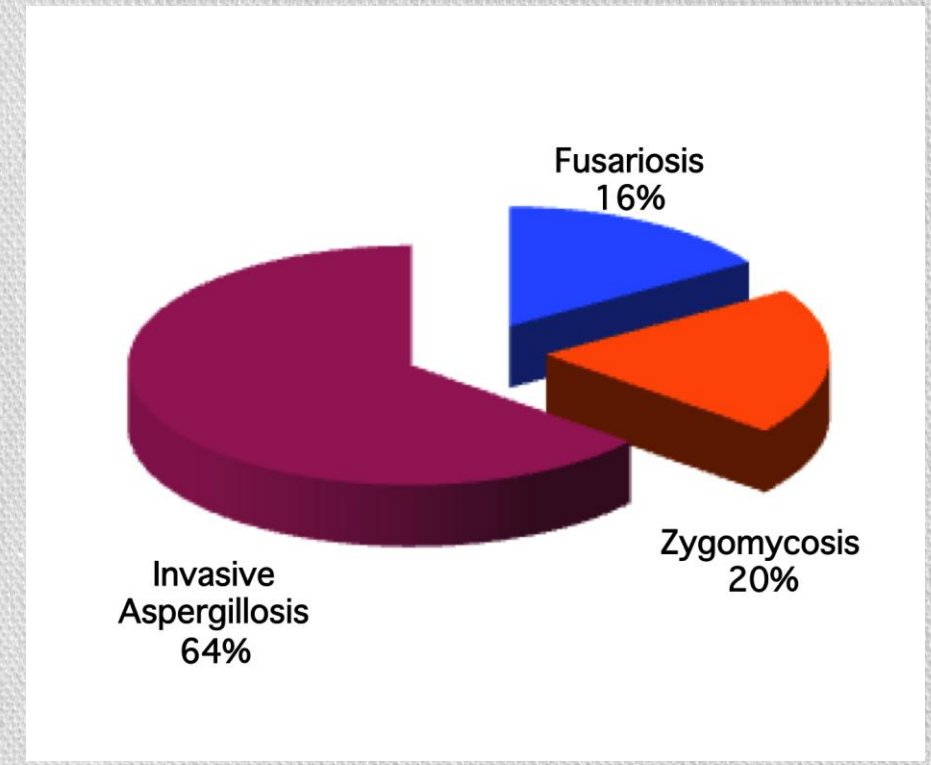
University Hospital

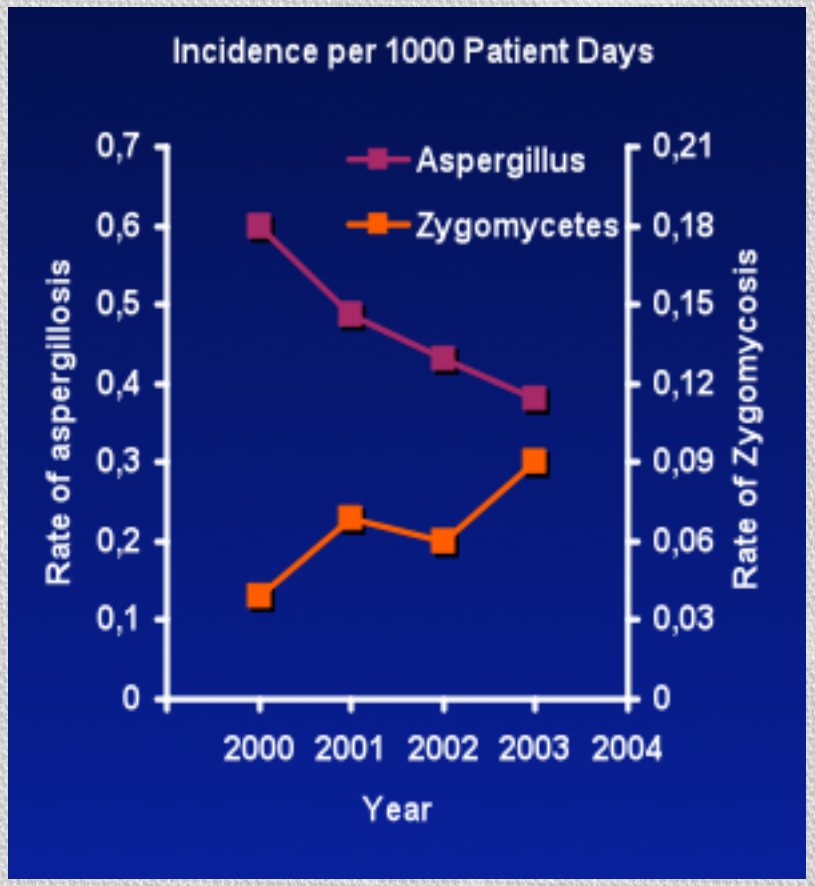


Hematology Department

CANDIDA ISOLATES IN A UNIVERSITY HOSPITAL BETWEEN YEARS 2002-2006. Özay Arıkan Akan, Hamdi Akan, Sevil Uysal

İnvazif küflerde değişme





Kontoyiannis DP, et al. J Infect Dis. 2005;191:1350

KİME?

En sık 4. patojen (kan akımı infeksiyonu) (ABD verisi)

			% BSI			% Crude Mortality		
Rank	Pathogen	BSI per 10,000 admissions	Total (n=20,978)	ICU (n=10,515)	Non-ICU (n=10,515)	Total	ICU	Non-ICU
1.	CoNS	15.8	31.3	35.9	26.6	20.7	25.7	13.8
2.	S aureus	10.3	20.2	16.8	23.7	25.4	34.4	18.9
3.	Enterococcus spp	4.8	9.4	9.8	9.0	33.9	43.0	24.0
4.	Candida spp	4.6	9.0	10.1	7.9	39.2	47.1	29.0
5.	E coli	2.8	5.6	3.7	7.6	22.4	33.9	16.9
6.	Klebsiella spp	2.4	4.8	4.0	5.5	27.6	37.4	20.3
7.	P aeruginosa	2.1	4.3	4.7	3.8	38.7	47.9	27.6
8.	Enterobacter spp	1.9	3.9	4.7	3.1	26.7	32.5	18.0
9.	Serratia spp	0.9	1.7	2.1	1.3	27.4	33.9	17.1
10.	A baumannii	0.6	1.3	1.6	0.9	34.0	43.4	16.3

BSI=blood stream infection.
SCOPE study. Wisplinghoff H, et al. Clin Infect Dis. 2004;39:309-317.

Table 2

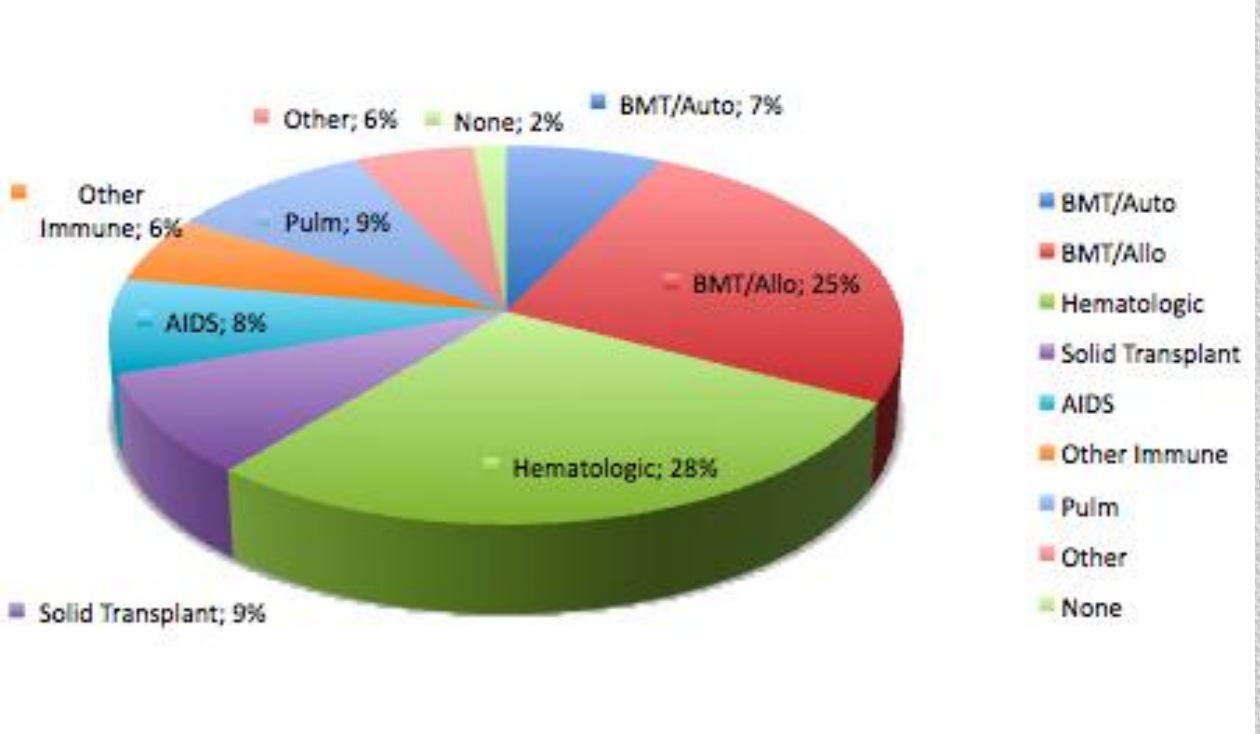
Underlying pathology/medical care of patients with candidaemia ($n = 2089$; more than one may be present in each episode)

	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

İnvazif Aspergillozlu hastalarda primer tanı

595 hasta



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

Avrupa'da İnvazif 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

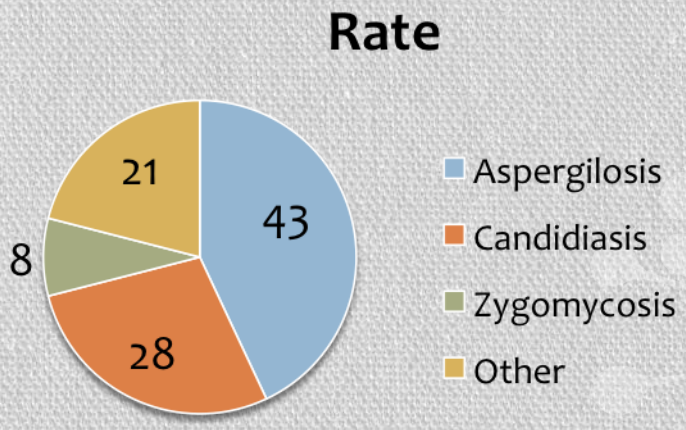
Pagano L, Haematologica 2006; 91(8):1068-73

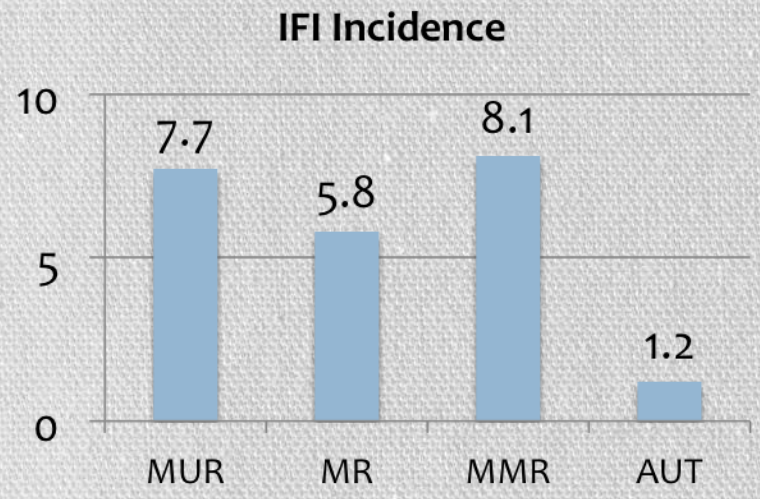
Pagano L, CID 2007:45 (1):1161-1170

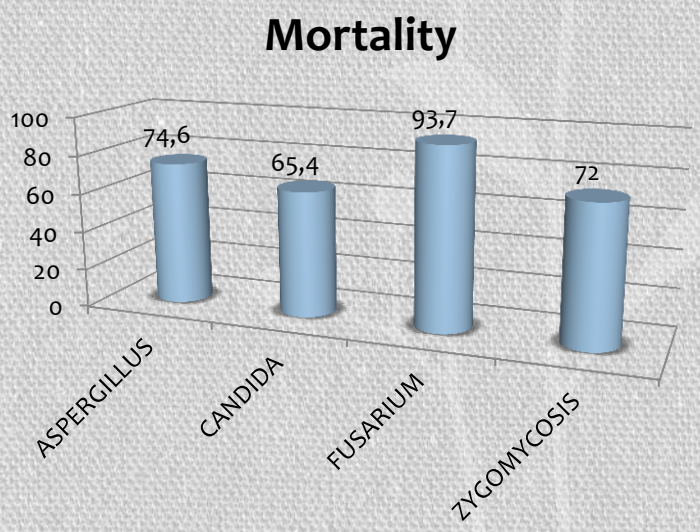
MORTALITE (%)	Allogeneic KHN	MR	MMR	MUR	Otolog KHN
Aspergillus	77.2	71	83	74	57.1
Candida	40				43.8
Other	40				-

ABD'de İnvazif fungal infeksiyonlar Transnet Verisi - 875 AHSCT

CID 2010

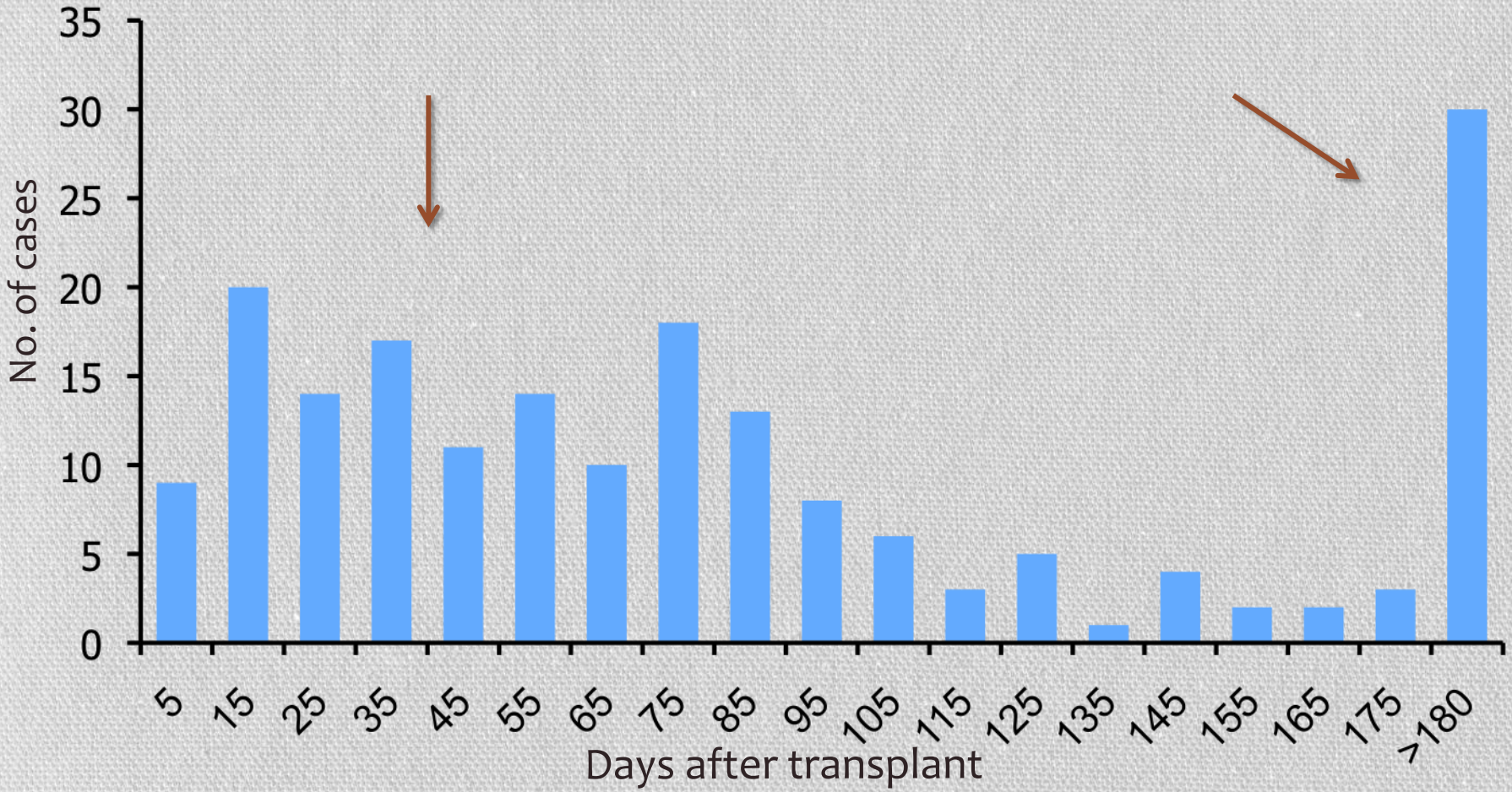






NE ZAMAN?

Allogeneik kök hücre nakli sonrası Aspergillosis 1993-1998

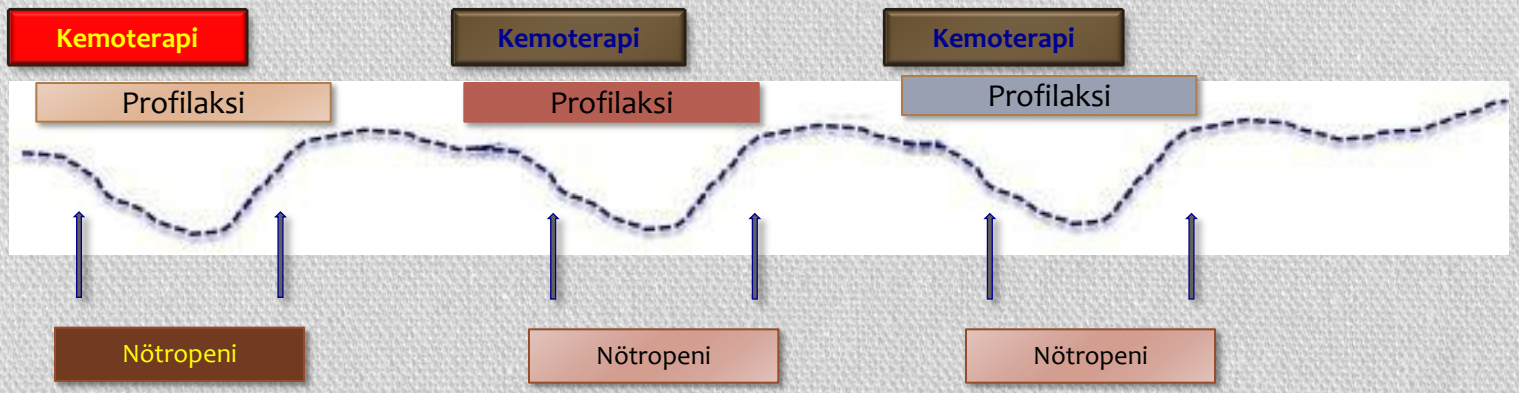


Marr KA, et al. Blood 2002;100:4358

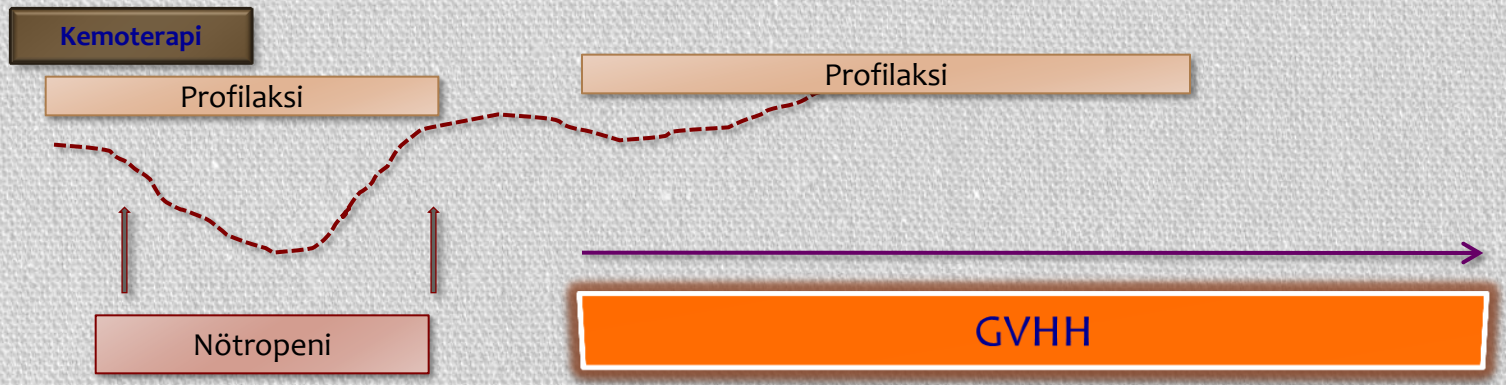
3 önemli risk grubu var

- İndüksiyon alan AML
- Erken fazda (nötropenik) allojeneik kök hücre nakli
- GVHH olan allojeneik kök hücre nakli

Akut Lösemi - MDS



Allojeneik KHN

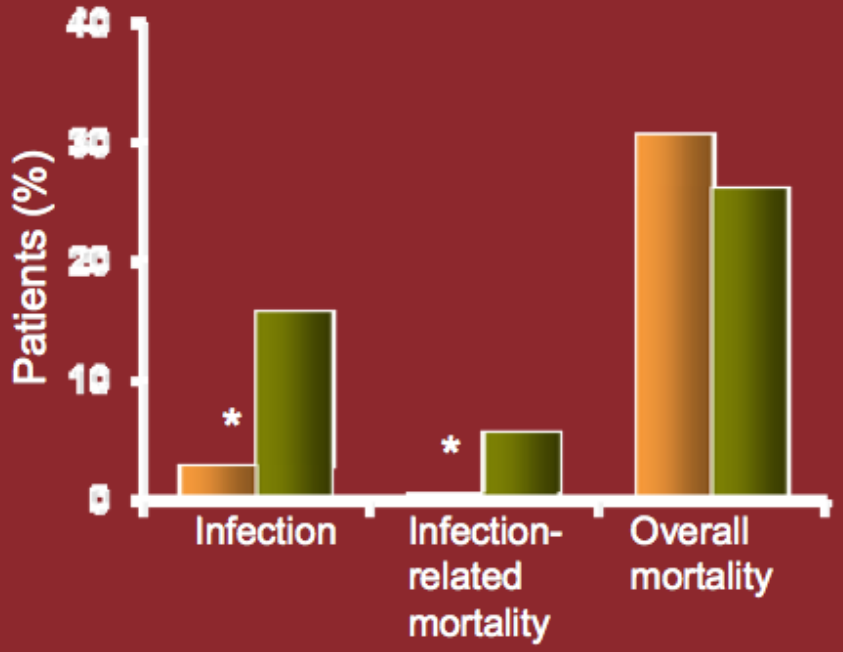


NEYLE ve NASIL?

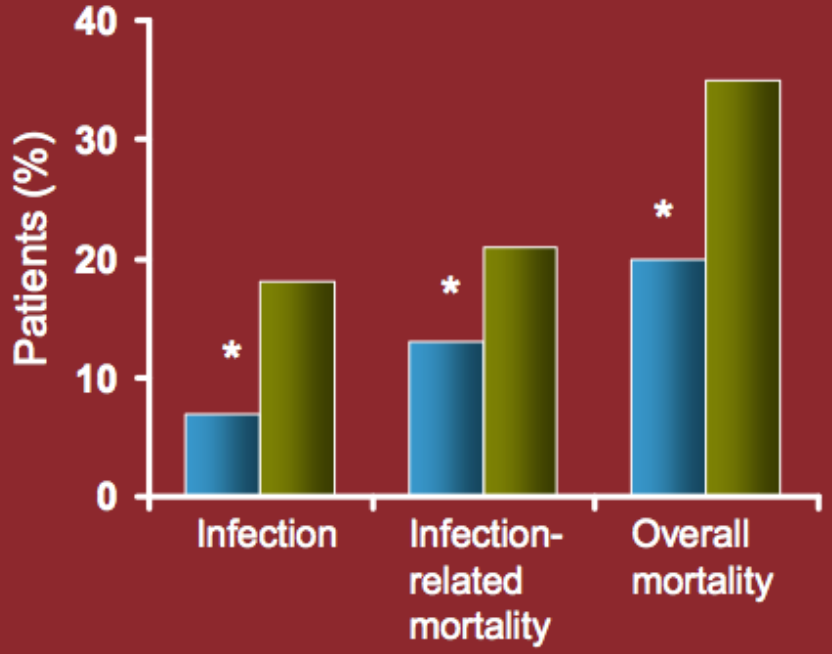
Fluconazole: Prophylaxis
(Pre-engraftment)

Fluconazole Placebo

52% Allografts/48% Autologous;
Fluconazole (400 mg/d) vs placebo → Engraftment[1]



88% Allografts/12% Autologous;
Fluconazole (400 mg/d) vs placebo → Day 75[2]



*Statistical significance between fluconazole and placebo.

1. Goodman JL, et al. *N Engl J Med*. 1992;326:845-851.
2. Slavin MA, et al. *J Infect Dis*. 1995;171:1545-1552.

Flukonazol Profilaksisi IFI sıklığını azaltır mı?

Grup	Doz	Etki	Kaynak
Allojeneik	400 mg qd	Kanıtlanmış IFI %18 → %7	Slavin 1995, Marr 2000
Otolog	400 mg qd	Bilinmiyor	Goodman 1992
AML	400 mg qd	Yok	Schaffner 1995
	400 mg qd	Kanıtlanmış/Olası %24 → %7	Rotstein 1999

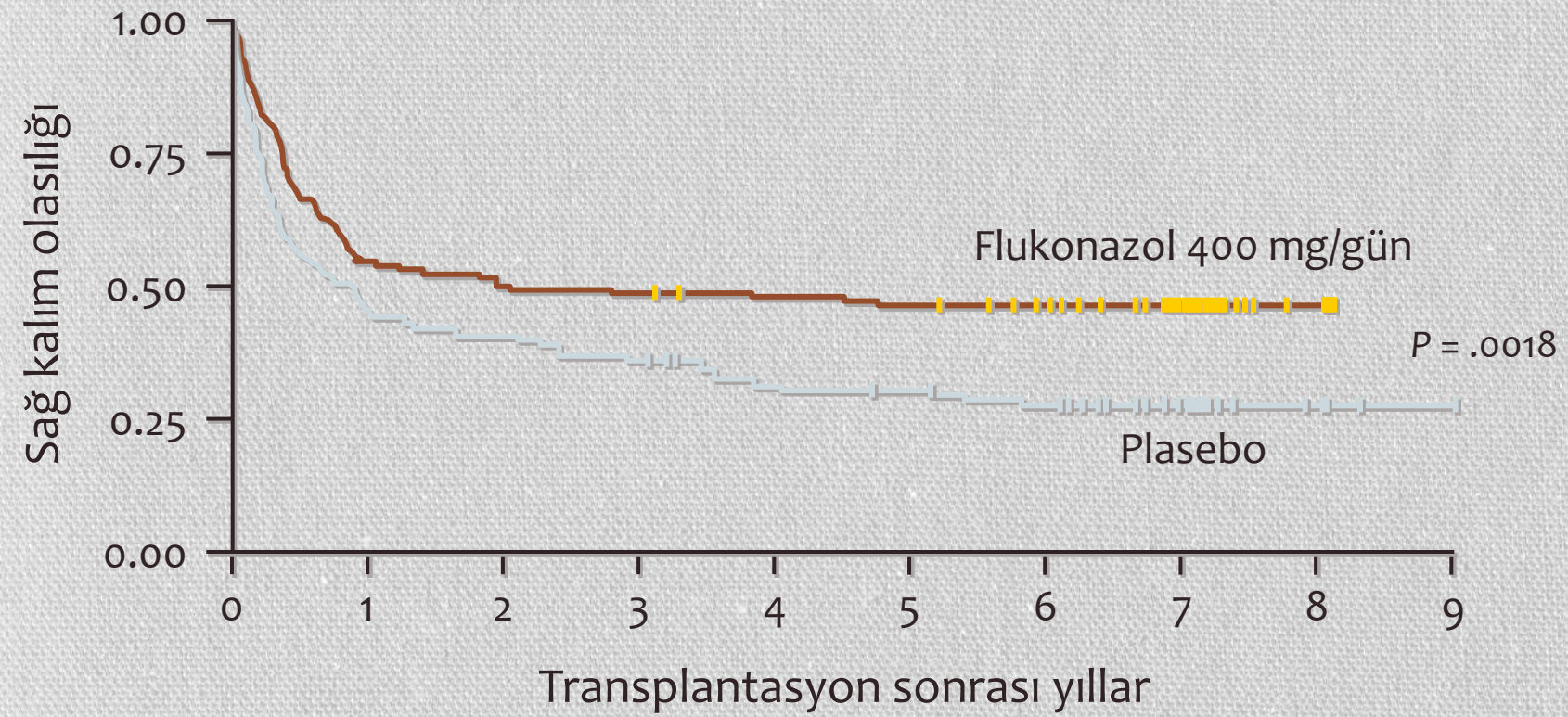
Allojeneik KHN' de flukonazol IFI sıklığını azaltır	**AI**
Otolog KHN' de flukonazol IFI sıklığını azaltır	CIII
AML' de flukonazol IFI sıklığını azaltır	AI

Flukonazol Profilaksisi IFI mortalitesini azaltır mı?

Grup	Doz	Etki	Kaynak
Allojeneik	400 mg qd	%21 → %13	Slavin 1995, Marr 2000
Otolog	400 mg qd	%5.6 → %0.6	Goodman 1992
AML	400 mg qd	yok	Schaffner 1995
	400 mg qd	%4.5 → %0.7	Rotstein 1999

Allojeneik KHN' de flukonazol IFI mortalitesini azaltır	**AI**
Otolog KHN'de flukonazol IFI mortalitesini azaltır	**AI**
AML' de flukonazol IFI mortalitesini azaltır	CIII

Proflaksi Uzun Süre Sağkalım



Marr KA, et al. *Blood*. 2000;96:2055.

Flukonazol Profilaksisi Ampirik AF kullanımını azaltır mı?

Grup	Doz	Etki	Kaynak
Allojeneik	400 mg qd	Ampirik AF kullanana kadar geçen süre: 18-21gün	Slavin 1995, Marr 2000
Otolog	400 mg qd	Bilinmiyor	Goodman 1992
AML	400 mg qd	Ampirik AF %33 → %48	Schaffner 1995
	400 mg qd	Ampirik AF %50 → %57	Rotstein 1999

Allojeneik KHN' de flukonazol ampirik AF kullanımını azaltır	AI
Otolog KHN' de flukonazol ampirik AF kullanımını azaltır	CIII
AML' de flukonazol ampirik AF kullanımını azaltır	EI

Flukonazol Profilaksisi genel mortaliteyi azaltır mı?

Grup	Doz	Sonuç	Kaynak
Allojeneik	400 mg qd	%55 - %28	Slavin 1995, Marr 2000
Otolog	400 mg qd	Yok	Goodman 1992
AML	400 mg qd	Yok	Schaffner 1995
	400 mg qd	Yok	Rotstein 1999

Allojeneik KHN' de flukonazol genel mortaliteyi azaltır	**AI**
Otolog KHN' de flukonazol genel mortaliteyi azaltır	CIII
AML' de flukonazol genel mortaliteyi azaltır	CIII

ITRAKONAZOL ORAL SOLÜSYONA KARŞI AMPHO-B KAPSÜL

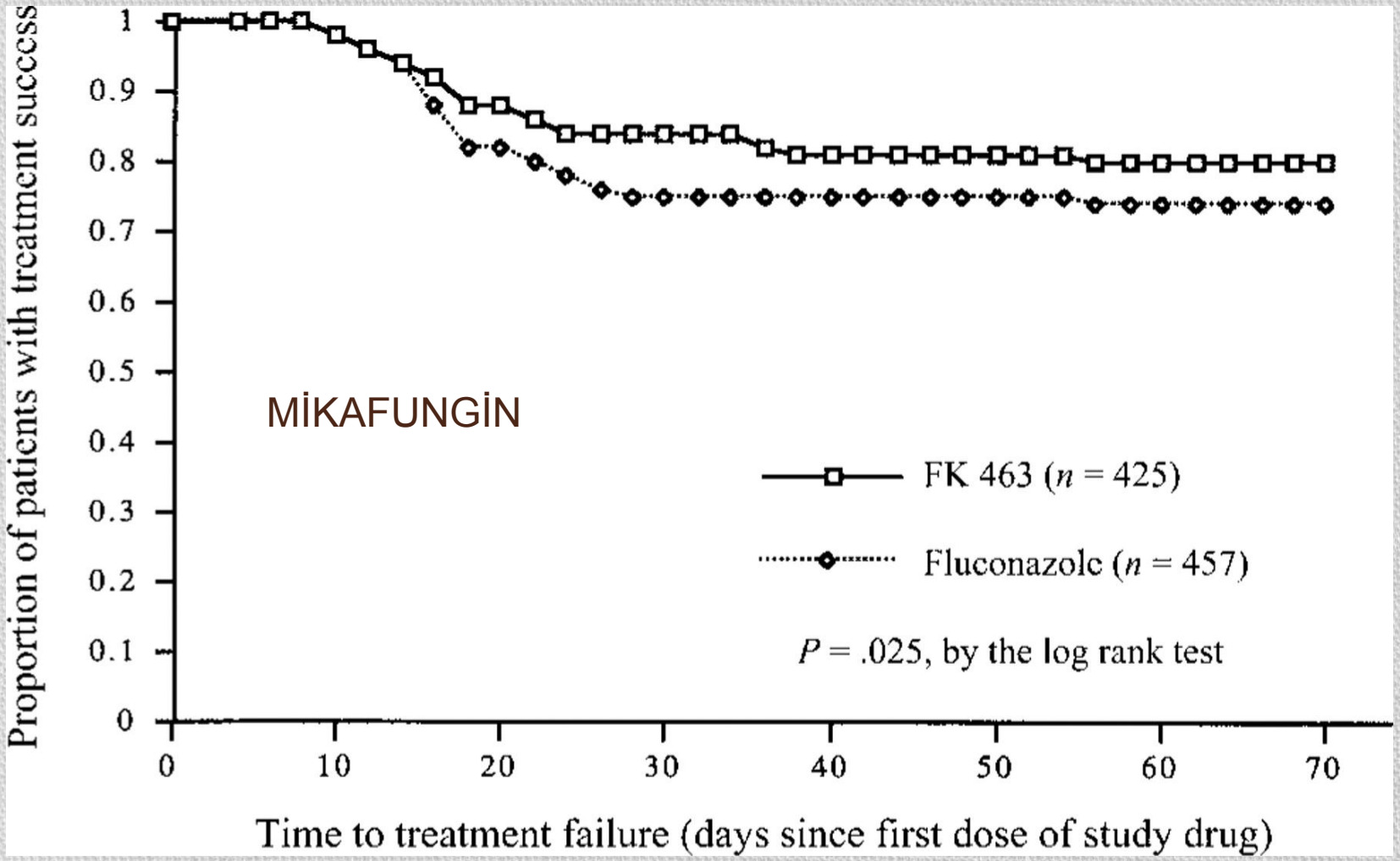
HAROUSSEAU et al. Antimicrob Ag Chemother 2000; 44:1887-93

ITRAKONAZOL ORAL SOLÜSYONA KARŞI PLASEBO

Menichetti et al. Clin Infect Dis 1999;28:250

Adverse event	Voriconazole N=234	Itraconazole N=255	P value
Vomiting	9 (4%)	40 (16%)	<0.01
Nausea	18 (8%)	38 (15%)	0.01
Diarrhea	10 (4%)	28 (11%)	<0.01
Headache	11 (5%)	13 (5%)	0.84
Visual impairment	14 (6%)	0 (0%)	<0.01
Hepatotoxicity/Liver function test abnormality	29 (12%)	12 (5%)	<0.01

Modified intent-to-treat analysis (i.e., patients received at least 1 dose of study drug) showing Kaplan-Meier estimates of the proportion of patients who received micafungin (FK 463) or Fluconazole and experienced treatment success, by time after initiation of study therapy.



van Burik J H et al. Clin Infect Dis. 2004;39:1407-1416

822 Kök hücre hastası

Mortalite farkı yok!

Aerosol Amfoterisin-B

- Öksürük yapıyor
- Optimal doz belli değil

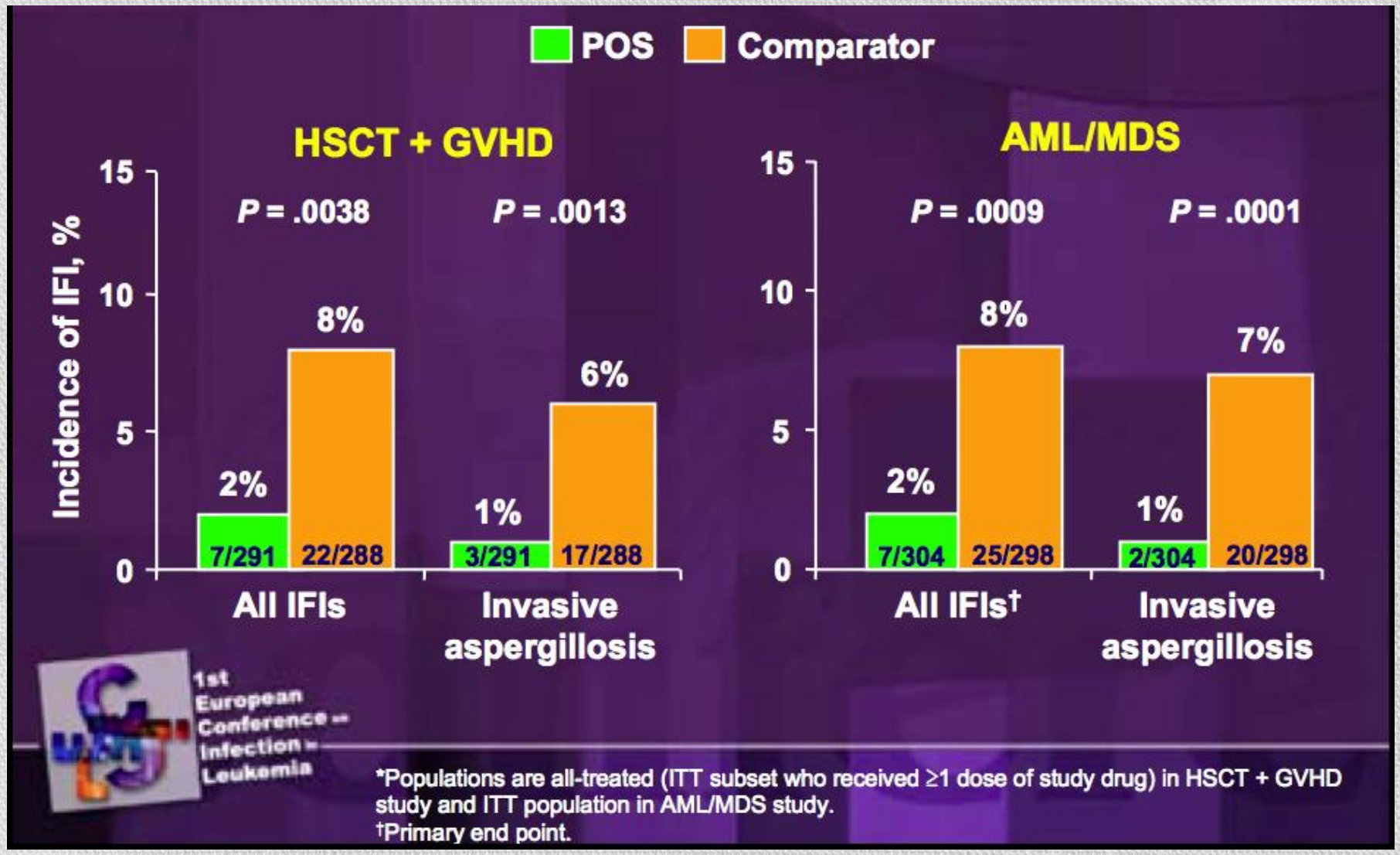
YENİ NE VAR?

POSAKONAZOL ÇALIŞMALARI

	Allo-GVHD/Ullmann	AML-MDS/Cornely
Tasarım	Çift kör	Randomize, tek kör
Hasta özellikleri	Akut veya kronik GVHD olan Allo KHN	Yeni tanı ya da relaps AML/MDS (kemoterapi, nötropeni)
Profilaksi	POS 200 mg oral susp. x3/gün vs. Flu 400 mg/gün	POS 200 mg oral susp. x3/gün vs. Flu 400 mg/gün veya ITZ 200 mgx2/gün
Süre	112 gün max.	Kemoterapi başından sonra 84 gün'e
İzlem	Tedavi bitiminden sonra 2 ay	Randomizasyon sonrası 100 gün

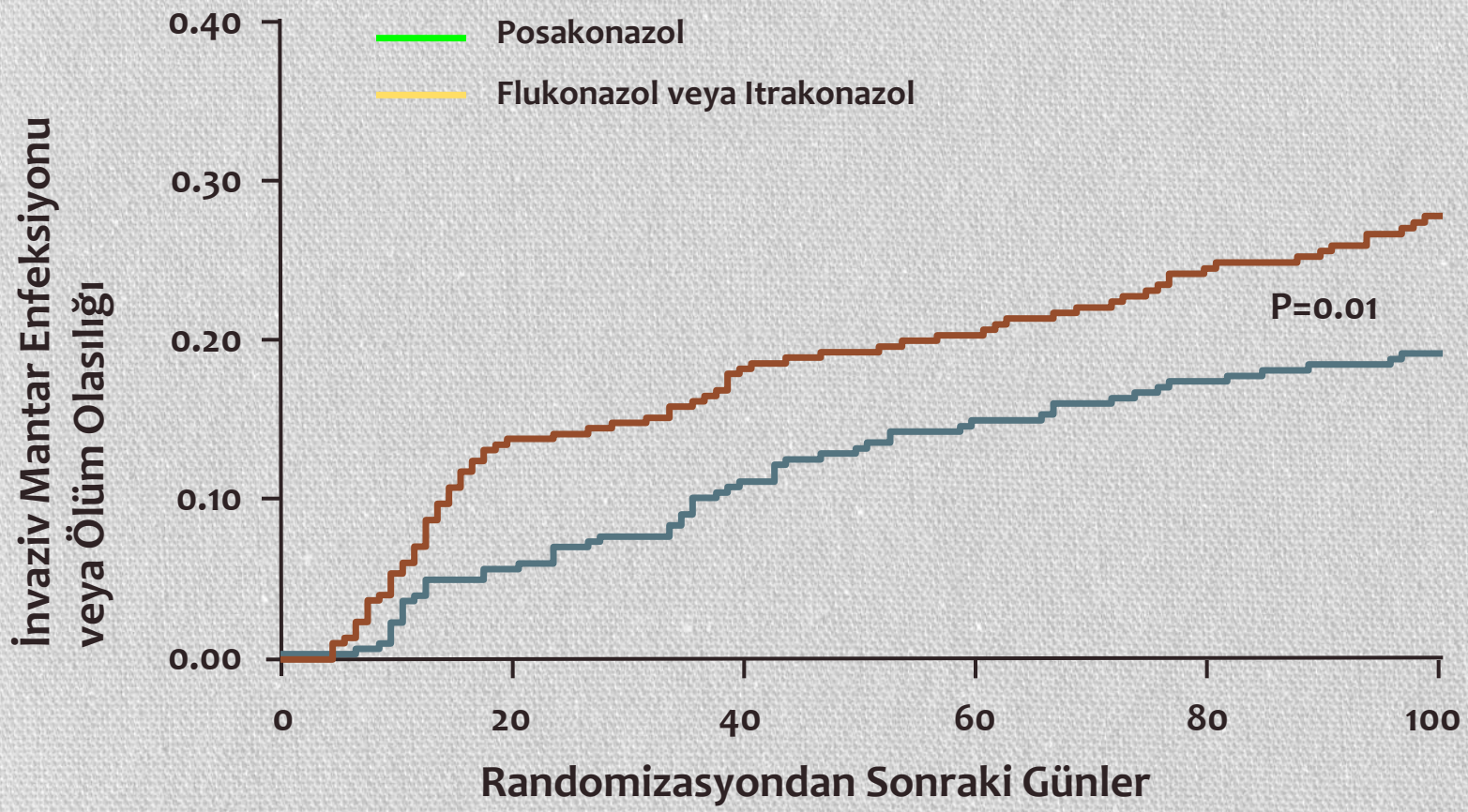
Ullmann et al. N Engl J Med 2007; 356: 335-347
Cornely et al. N Engl J Med 2007; 356: 348-359

Tedavi sırasında olası/kanıtlanmış IFI sıklığı



Nötropenik Hastalarda Posakonazol Profilaksisi

Bulgular – İnvaziv Mantar Enfeksiyonu veya Ölüme Kadar Geçen Süre



Cornely OA et al. *N Engl J Med*. 2007;356:348-359.

	ECIL III 2009		IDSA 2008	BSH 2008
Allogeneik KHN	Nötropeni	GVHD		
Flukonazol	A I	CI		
İtrakonazol	B I[1,2]		B I	A I
Posakonazol	Veri yok	A I[3]	A I	A I
Vorikonazol	Provizyonel AI	Provizyonel AI		
Micafungin	C I	Veri yok		
Polien	C I[3]	C I[3]		B II
Aerosol liposomal Ampho-B + oral Flukonazol	BII	Yetersiz data		
Akut lösemi induksiyon			AML & MDS	
Flukonazol	C I			
İtrakonazol	C I[1,2]		B I	A I
Posakonazol	A I[3]		A I	A I
Polien	C I			B II
Aerosolized liposomal Ampho-B + oral Flukonazol	BI			
	1. interaksiyon/intolerans 2. Monitor serum kons. 3. Düşük doz			İlaç Risk of Drug interaction for azoles Sekonder Profilaksi +

VORİKONAZOL ÇALIŞMALARI

1- Wingard J et al. ASH 2007 Oral Session
Results of a Randomized, Double-Blind Trial of Fluconazole (FLU) vs. Voriconazole (VORI) for the Prevention of Invasive Fungal Infections (IFI) in 600 Allogeneic Blood and Marrow Transplant (BMT) Patients

2 – Marks D et al. ICAAC 2009, San Francisco, M-1249a
Voriconazole (VOR) versus itraconazole (ITR) for primary prophylaxis of invasive fungal infections in allogeneic HSCT recipients

Results of a Randomized, Double-blind Trial of Fluconazole (FLU) vs. Voriconazole (VORI) for the Prevention of Invasive Fungal Infections (IFI) in 600 Allogeneic Blood and Marrow Transplant (BMT) Patients

John R Wingard, Shelly L Carter, Thomas J Walsh, Joanne Kurtzberg, Trudy N Small, Iris D Gersten, Adam M Mendizabal, Helen Leather, Dennis L Confer, Lindsey R Baden, Richard T Maziarz, Edward A Stadtmauer, Javier Bolanos-Meade, Janice Brown, John F DiPersio, Michael Boeckh and Kieren A Marr

UPDATE ECIL- 3 2009

Microbiologically Documented Proven/Probable Fungal Infections Through Day 180

Fungal Genus	FLU	VORI
• Aspergillus*	16*	7*
• Candida	3	3
• Zygomycetes	3	2
• Other	1	1
Totals**	23**	13**

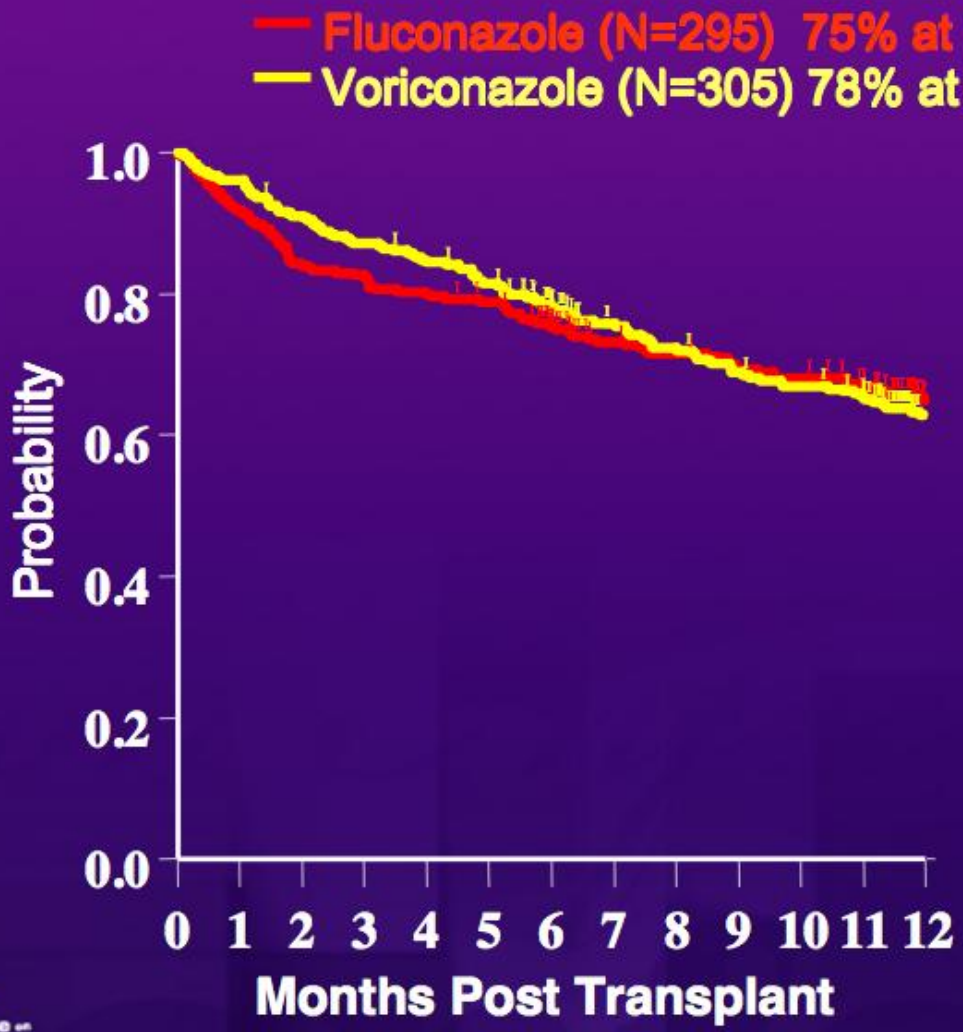
*p = 0.05 ** p = 0.11

3rd European Conference on Infections in Leukemia

Wingard J et al. 2007

UPDATE ECIL- 3 2009

Fungal-free Survival



3rd European Conference on Infections in Leukemia

Wingard J et al. 2007

Vori ve Flu

Wingard et. al.

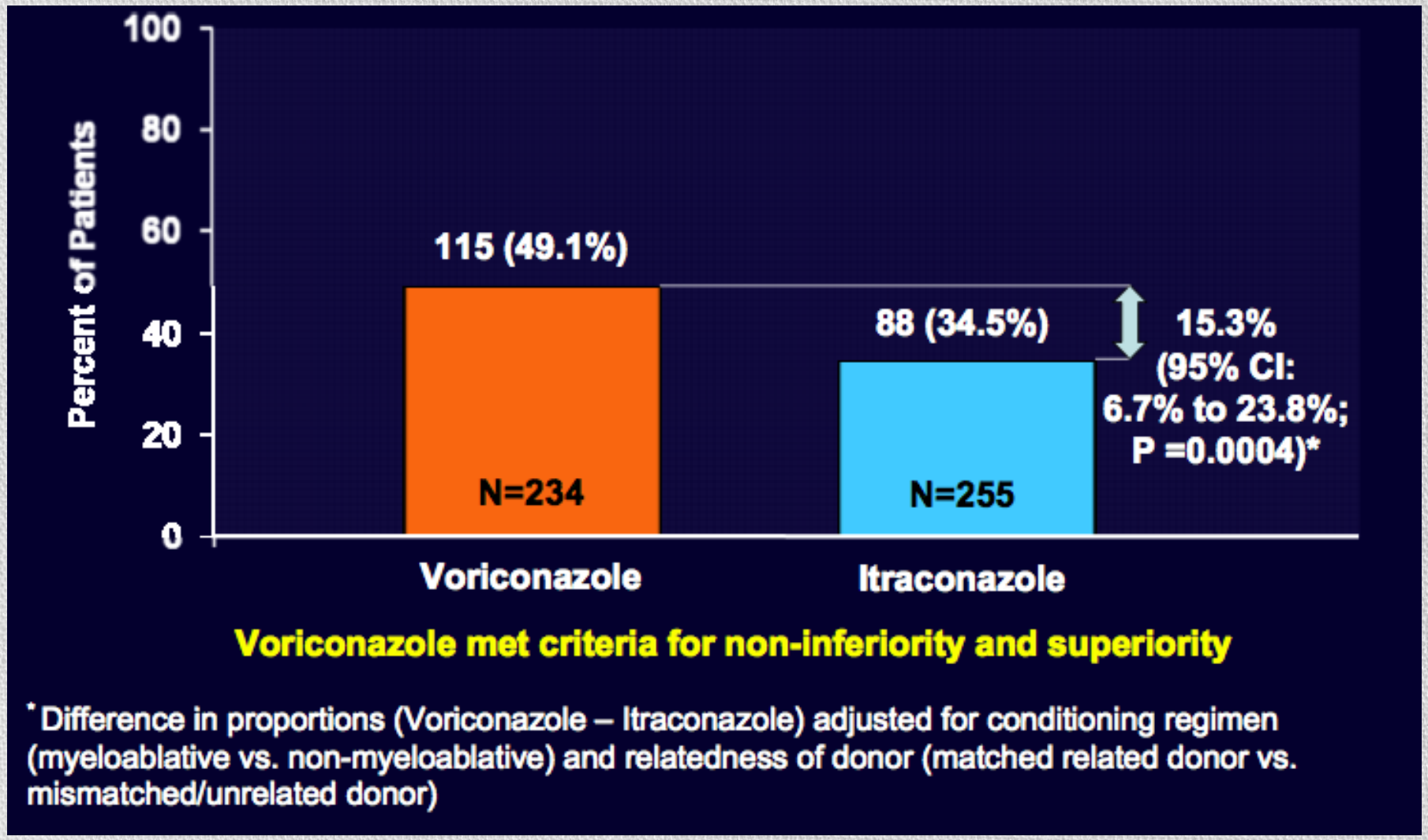
- Genel sağkalım ve IFI'siz sağkalımda fark yok
- Vorikonazol kolunda daha az Aspergillus infeksiyonu
- Zigomiçetes'de artış yok
- Benzer toksisite

Voriconazole vs Itraconazole for Primary Prophylaxis of Invasive Fungal Infection (IFI) in Allogeneic Hematopoietic Cell Transplant (HCT) Recipients

D. I. MARKS[1], C. KIBBLER[2], A. PAGLIUCA[3], P. RIBAUD[4], C. SOLANO[5], C. P. HEUSSEL[6], G. COOK[7], A. GLASMACHER[8], H. SCHLAMM[9], M. KANTECKI[9], Improvit Study Group;

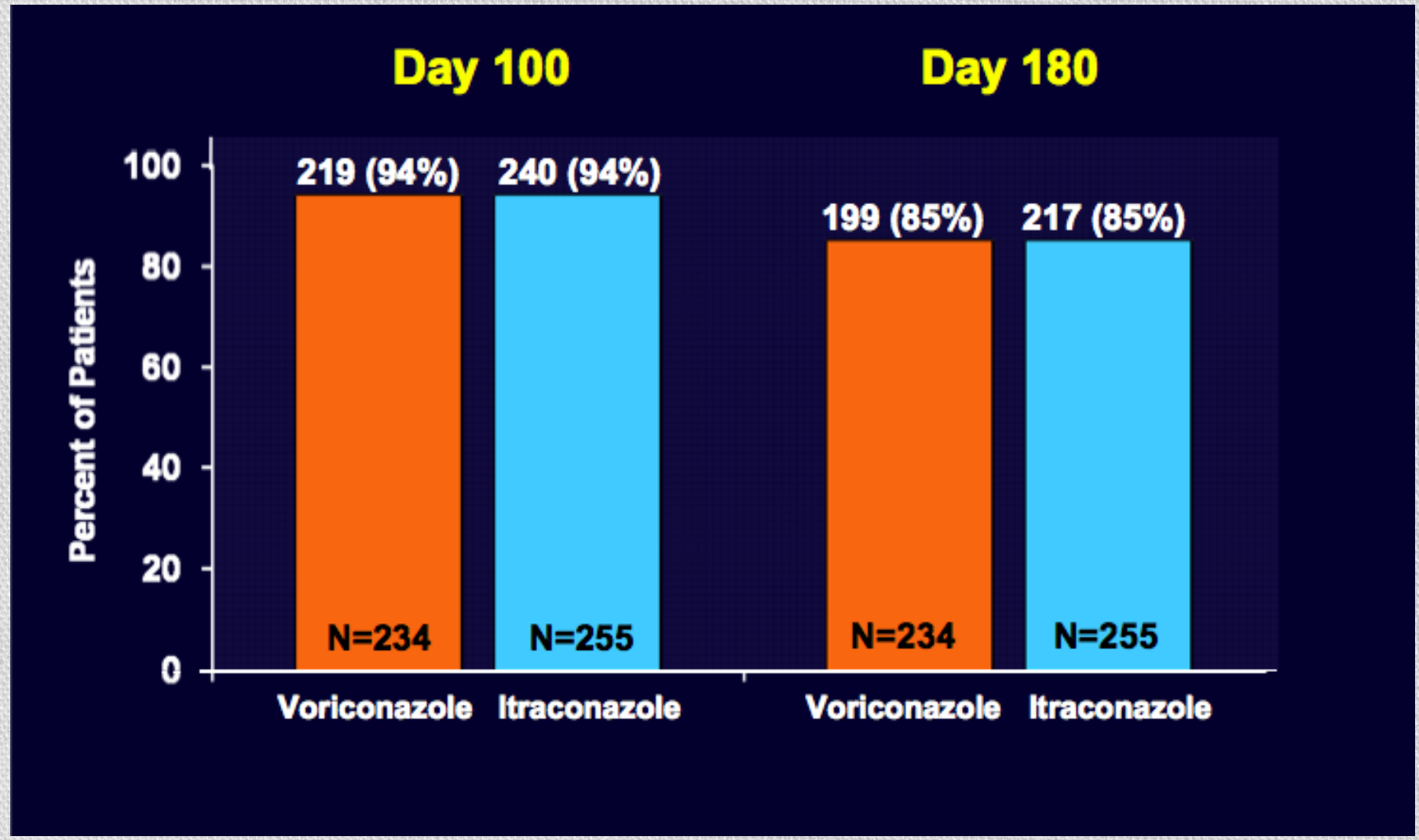
[1]UH Bristol, Bristol, United Kingdom, [2]Royal Free H, London, United Kingdom, [3]King's Coll H, London, United Kingdom, [4]H Saint-Louis, Paris, France, [5]H Clínico, Valencia, Spain, [6]Radiology, Thoraxklinik at Univ H, Heidelberg, Germany, [7]St James' Univ H, Leeds, United Kingdom, [8]Univ klinikum Bonn, Bonn, Germany, [9]Pfizer Inc, New York, NY.

180. günde profilakside başarı



*Difference in proportions (Voriconazole – Itraconazole) adjusted for conditioning regimen (myeloablative vs. non-myeloablative) and relatedness of donor (matched related donor vs. mismatched/unrelated donor)

Sağkalım


Day 100
Day 180
Percent of Patients
100
80
60
40
20
0
219 (94%)
240 (94%)
199 (85%)
217 (85%)
N=234
N=255
N=234
N=255
Voriconazole
Itraconazole
Voriconazole
Itraconazole

Profilaksi Kılavuzları

	ECIL III 2009		IDSA 2008	BSH 2008
Allogeneik KHN	Nötropeni	GVHD		
Flukonazol	A I	CI		
İtrakonazol	B I[1,2]		B I	A I
Posakonazol	Veri yok	A I[3]	A I	A I
Vorikonazol	Provizyonel AI	Provizyonel AI		
Micafungin	C I	Veri yok		
Polien	C I[3]	C I[3]		B II
Aerosol liposomal Ampho-B + oral Flukonazol	BII	Yetersiz data		
Akut lösemi induksiyon			**AML & MDS**	
Flukonazol	C I			
İtrakonazol	C I[1,2]		B I	A I
Posakonazol	A I[3]		A I	A I
Polien	C I			B II
Aerosolized liposomal Ampho-B + oral Flukonazol	BI			
	1. interaksiyon/intolerans 2. Monitor serum kons. 3. Düşük doz			İlaç Risk of Drug interaction for azoles Sekonder Profilaksi +

Profilaksi Sorunları

- Azol toksisitesi
- Serum düzey izlenmesi
- İlaç etkileşimleri
- Azollere direnç
- Yeni mantarlar

AZOLLER: Diğer ilaçlarla etkileşim

Kullanılmamalı:
-rifabutin
-omeprazole
-phenytoin

Doz ayarı gerekli:
-warfarin
-cyclosporin
-takrolimus
-sulfonureler
-statinler
-benzodiazepin
-vinca alkaloidleri
-antrasiklinler?
-fentoin?

Kısmen kontrendike:
-astemizole
-barbiturates
(uzun etkili)
-karbamazepin
-cisapride
-pimozide
-kinidine
-rifampicin
-sirolimus
-terfenadine

Sekonder Profilaksi

- İyi dokümente edilmiş ve tamamen iyileşmiş bir IFI ardından yeni bir kemoterapi alacaklarda

Öneri:

AII

- Spesifik bir ilaç önerisi yok ancak bir önceki IFI episodunu dikkate al

ECIL-III

Kök hücre nakli yapılacak hastalarda:

- Daha önce invazif Aspergilloz gösterilen hastalarda küflere yönelik profilaksi

A-III

- En az 2 hafta nötropeni beklenen hastalar

C-III

- KHN öncesi uzun süren bir nötropeni dönemi

C-III

IDSA-2011

SONUÇ

- Antifungal profilaksi kime?
  - Akut lösemi/MDS indüksiyon fazı
  - Allojeneik kök hücre nakli GVHH dönemi
  - Allojeneik nakil erken dönemi ?
  - Otolog nakilde gerekli değil
- Candida için Flukonazol yeterli
- Asperillus için Posakonazol uygun, Vorikonazol ?
- İtrakonazol sorunlu
- Posa, İtra ve Vori serum düzeyi önemli
- Azol profilaksisi yapılanlarda tedavide azol?
- Azollerde İlaç etkileşimlerini unutma

TEŞEKKÜR EDERİM..