Değişen Fungal Epidemiyoloji ve Antifungal Direnç

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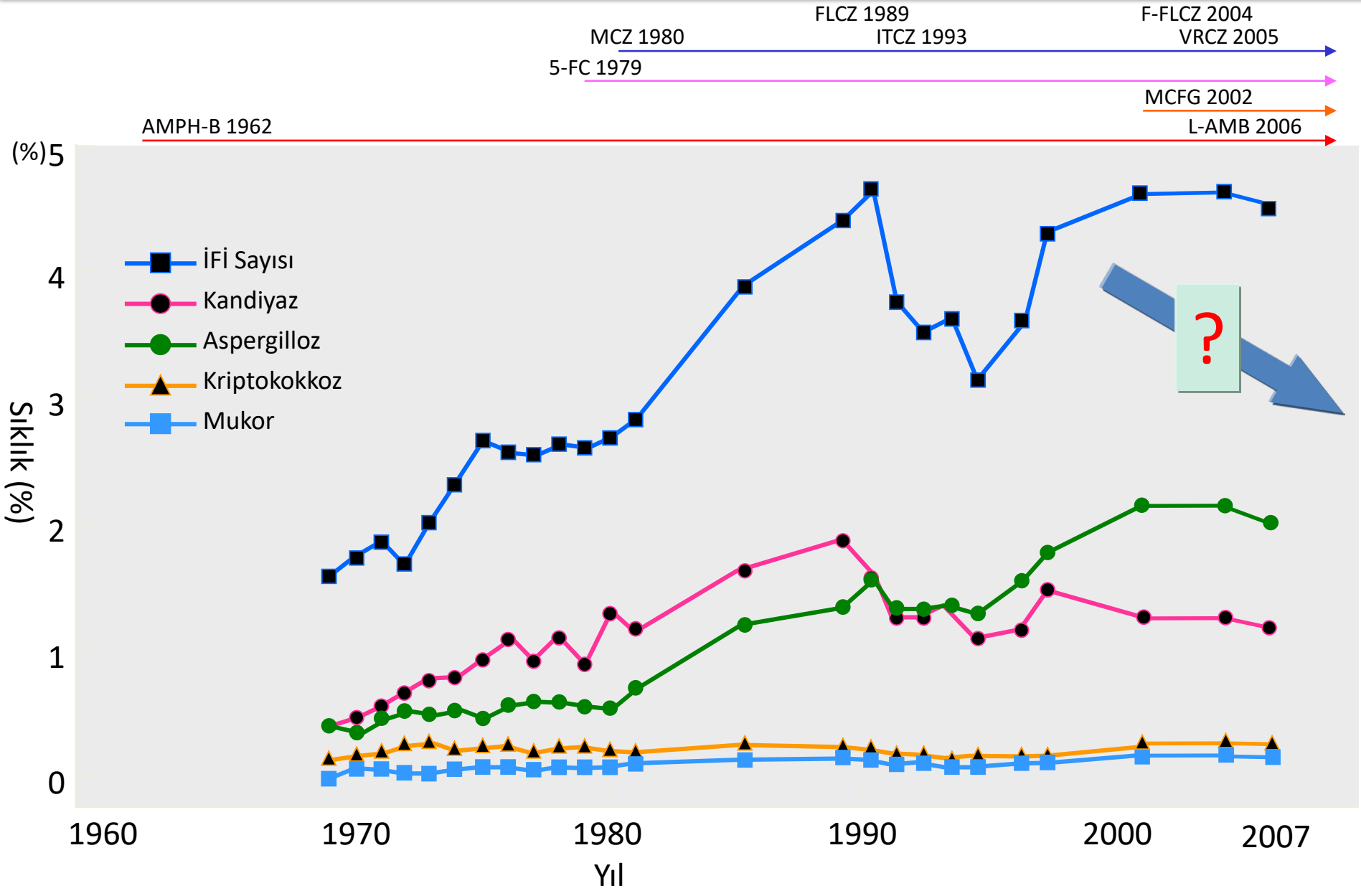
İnfeksiyon Hastalıkları ve
Klinik Mikrobiyoloji Anabilim Dalı

Konuşma Taslağı

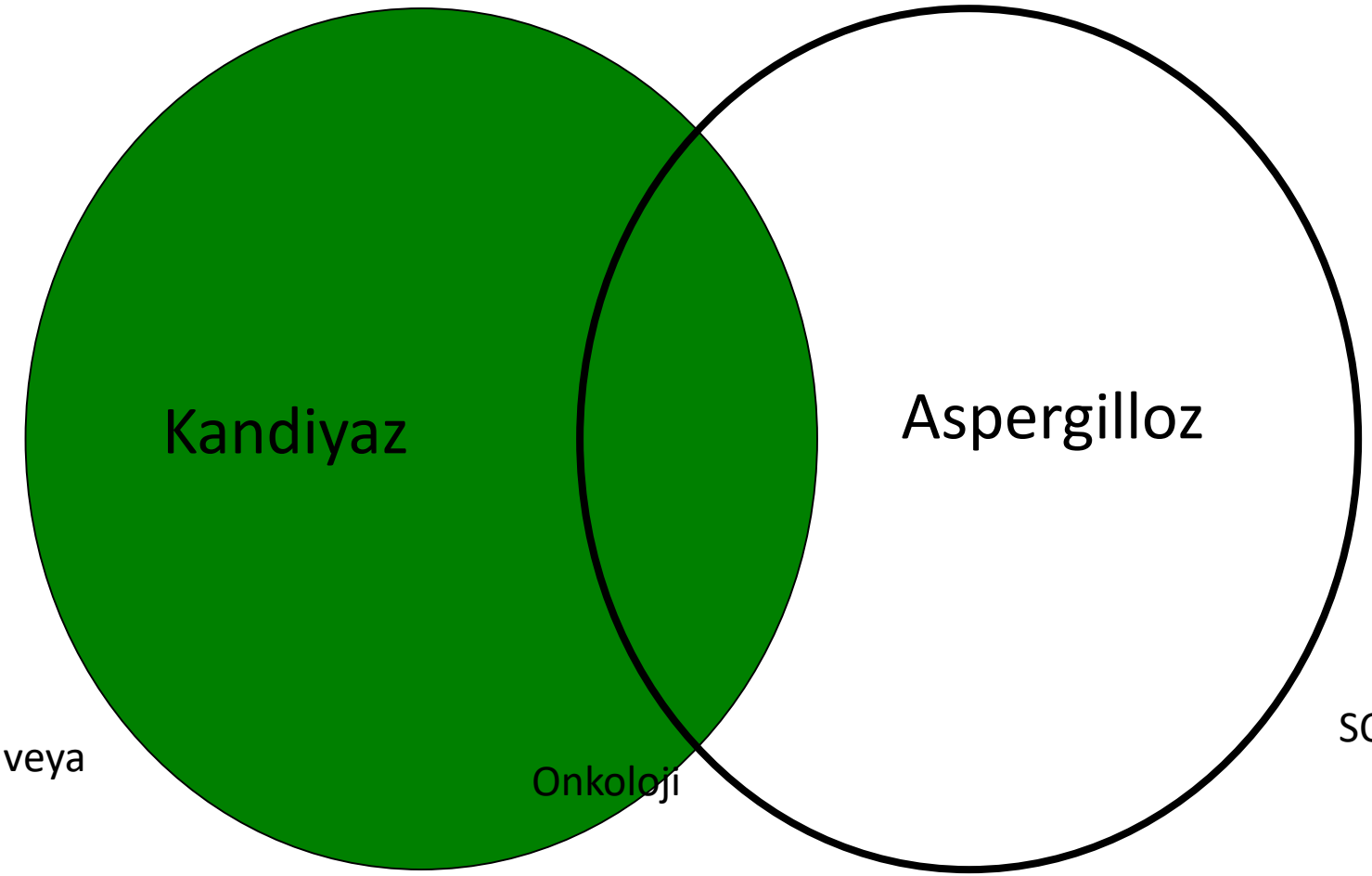
- Dünya'da Fungal İnfeksiyonların Epidemiyolojisi
- Antifungallere Direnç
- Dünya'da son durum
- Türkiye'de son durum
- Direnç Mekanizmaları
  - Risk Faktörleri
  - Kandida
  - Küfler

Otopsi Sonuçları: Sistemik Mantar Sıklıkları



Kume et al. Med Mycol J 52: 117-127, 2011

İnvazif Mikoz



MICU veya SICU

Onkoloji

SOT veya KİT

Bariyer immünitesi

İmmünitenin azalması

Bariyer + hücresel immünite

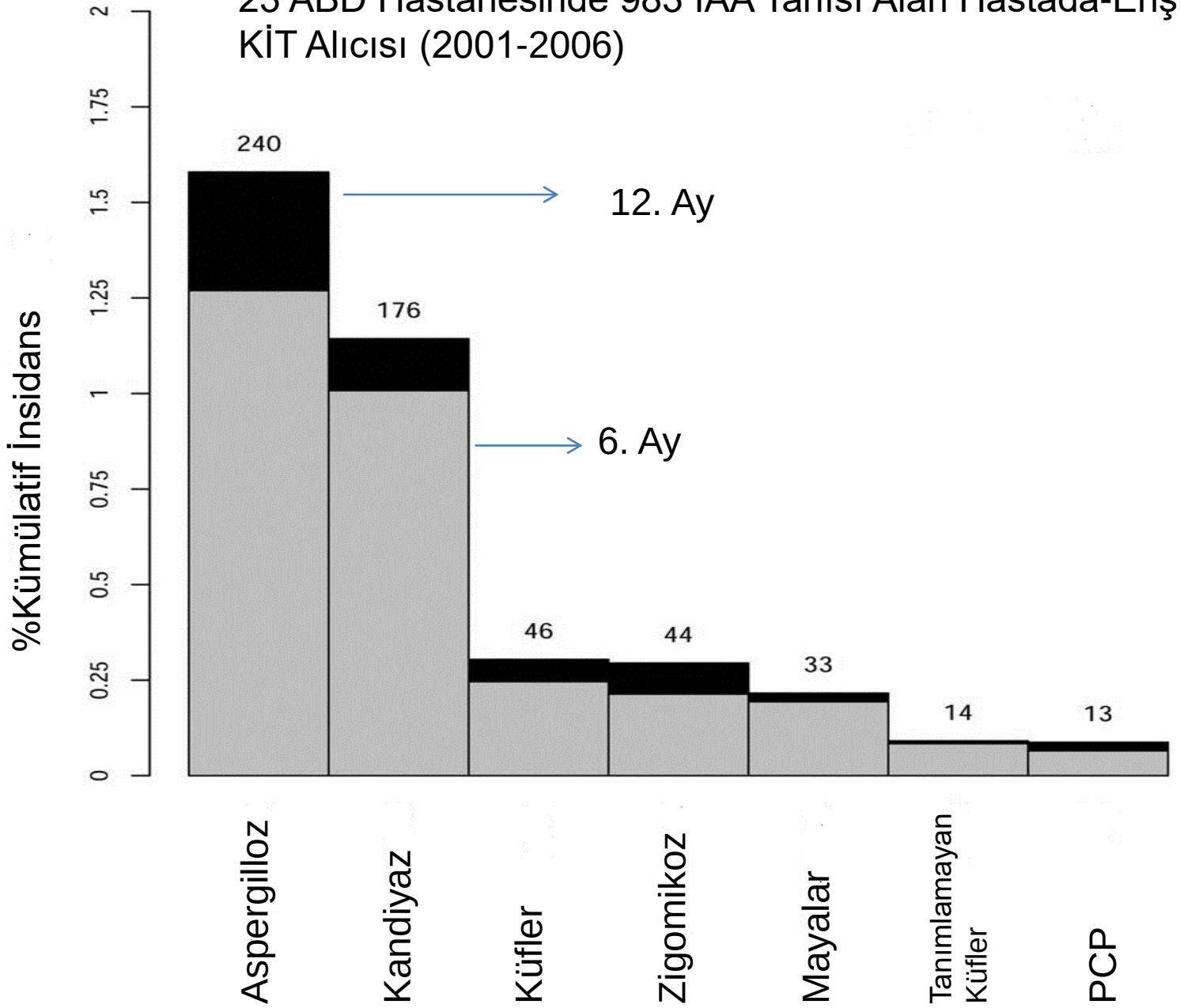
Klinik Epidemiyolojik Veri (ABD)

Altta Yatan hastalıklar(960 hasta) (2004-2008)

1.	Hematolojik Malignite	464	% 48.3
2.	Solid organ transplantı	280	% 29.2
3.	Kök hücre transplant	268	% 27.9
4.	HIV/AIDS	14	% 1.5
5.	İmmün yetmezlik	4	% 0.4
6.	Diğer	22	% 2.3

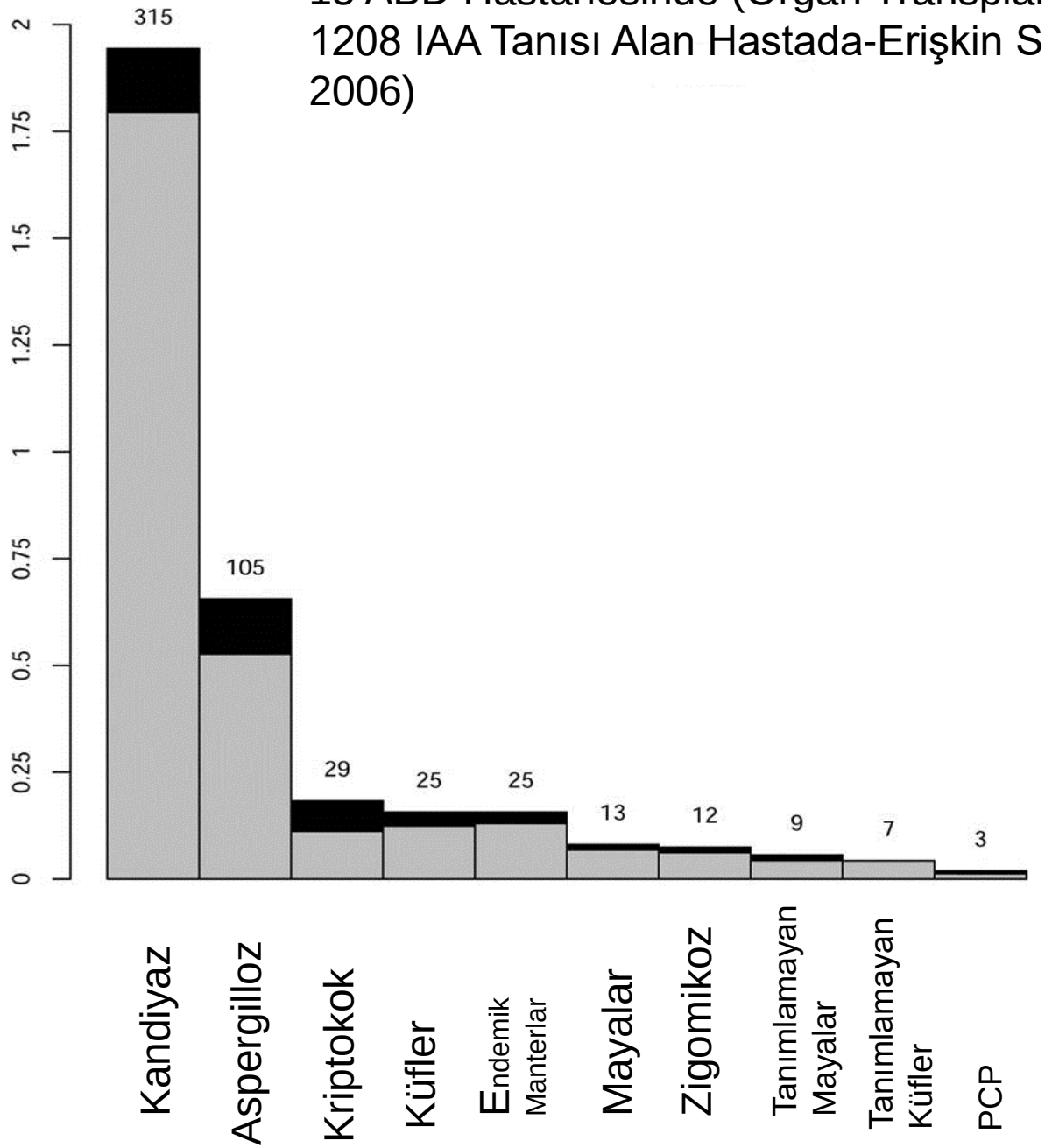
Steinbach WJ et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect 2012, 65, 453-464

23 ABD Hastanesinde 983 IAA Tanısı Alan Hastada-Erişkin KİT Alıcısı (2001-2006)



D. Kontoyiannis et al., CID 2010, 50:

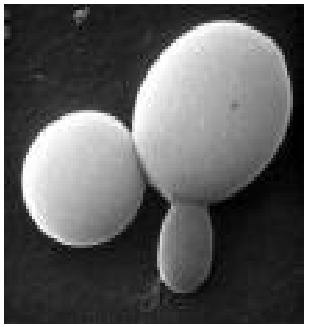
15 ABD Hastanesinde (Organ Transplantasyon Merkezi) 1208 IAA Tanısı Alan Hastada-Erişkin SOT Alıcısı (2001-2006)



P. Pappas et al., CID 2010, 50: 1101-1111

Kandiyaz

- İnvazif Kandida İnfeksiyonları:
  - ABD'de en sık 4. nozokomiyal dolaşım yolu infeksiyonu; kateterle ilişkili kandidemilerin yaklaşık %40'ını oluşturmaktadır.*



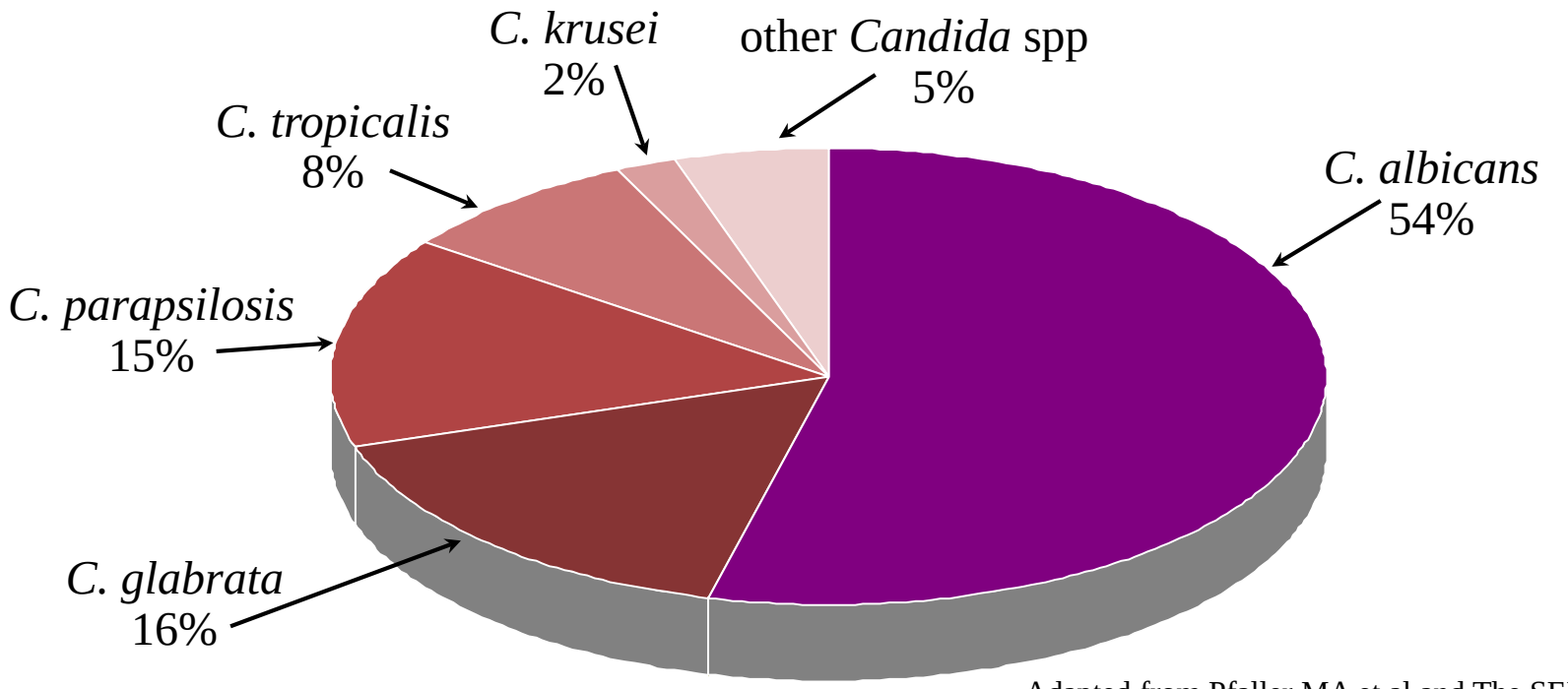
Patojen	**İzolat Sayısı**	**İnsidansı (%)**
KNS	3908	31.9
Staphylococcus aureus	1928	15.7
Enterococci spp.	1354	11.1
***Candida* species**	**934**	**7.6**

*In a 3-year (1995–1998) surveillance study of 49 hospitals in the United States.

Adapted from Edmond MB et al *Clin Infect Dis* 1999;29:239–244; Andriole VT *J Antimicrob Chemother* 1999;44:151–162; Uzun O, Anaissie EJ *Ann Oncol* 2000;11:1517–1521.

Dolaşım Yolu İnfeksiyonlarında En Sık İzole Edilen Kandida Türü Mantarların Türleri

Bir uluslar arası sürveyans çakışması: 1997-1998:



Adapted from Pfaller MA et al and The SENTRY Participant Group *Antimicrob Agents Chemother* 2000;44:747–751.

Since then increase in *Candida* spp. with higher incidence of fluconazole resistance.
Snydman DR. 2003. Chest 123(Suppl 5):500S-503S). Garbino J. et al. 2002. Medicine;81:425-433.

TABLE I. **Epidemiology and species distribution of fungaemia in Denmark in 2010 and 2011 compared with the previous 6-year period.**

	2004–09[a]	2010	2011	In total 2010–11
Fungal isolates (no.)	2901	505	576	1081
Episodes (no.)	2820	488	559	1047
Patients (no.)	2694	467	528	995
Median age (years (range and interquartile ages))	66 (0–98 and 55;74)	67 (0–96 and 55;75)	66 (0–105 and 57;75)	66 (0–105 and 56;75)
Gender (% males)	56.5	59.6	59.4	59.5
Episode rate per 100 000 inhabitants	8.6	8.8	10.1	9.4
Episode rate per 10 000 discharges	4.1	4.1	4.6	4.4
Species distribution				
Candida albicans	57.1%	52.9%	51.4%	52.1%
Candida dubliniensis	2.6%	1.8%	1.7%	1.8%
Candida glabrata	21.1%	26.9%	29.0%	28.0%
Candida krusei	4.1%	5.0%	4.7%	4.8%
Candida parapsilosis	3.7%	5.1%	3.3%	4.2%
Candida tropicalis	4.8%	4.0%	4.2%	4.1%
Candida species[b]	2.7%	2.4%	4.2%	3.3%
Non-*C. albicans* spp. not referred for ID[c]	2.4%	0.0%	0.0%	0.0%
Other fungi[d]	1.6%	2.0%	1.6%	1.8%

[a]Compiled from Arendrup *et al.* [1]

[b]*Candida* spp. includes the following species in 2010–11: *C. guilliermondii* 6, *C. inconspicua* 1, *C. kefyr* 6, *C. lambica* 1, *C. lusitaniae* 11, *C. magnolia* 1, *C. norvegensis* 4, *C. orthopsilosis* 2, *C. palmioleophila* 2 and *C. pelliculosa* 2.

[c]Non-*albicans* denotes isolates that were not *C. albicans* but not referred to the mycology reference laboratory for species identification.

[d]Other fungi includes: *Cryptococcus neoformans* 4, *Fusarium oxysporum* 1, *Fusarium proliferatum* 2, *Fusarium solani* 2, *Fusarium* sp. 1, *Geotrichum candidum* 1, *Rhodotorula glutinis* 1, *Saccharomyces boulardii* 1 and *Saccharomyces cerevisiae* 6.

TABLE 2. Incidence rate (per 100 000 inhabitants) and species distribution by age and gender in the 2-year period 2010–11

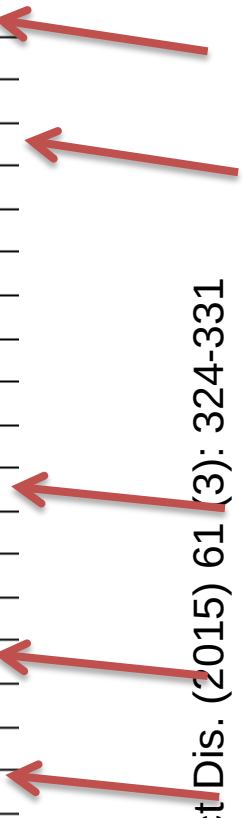
	Age group (years)											
	<1	1–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+	In total
Incidence	12.65	1.09	0.86	1.31	3.14	5.10	11.51	20.29	38.17	36.82	25.36	55.56	9.4
Female 2010–11	12.93	0.69	0.74	0.79	1.77	4.36	9.25	15.89	30.61	24.04	16.47	66.05	7.83
Male 2010–11	10.76	1.49	0.98	1.84	4.47	5.82	13.80	24.84	48.10	57.68	53.86	0.00	11.69
p value (Chi square approximation)	NS	NS	NS	NS	0.0055	NS	0.0139	0.0003	<0.0001	<0.0001	0.0136	NS	<0.0001
No. isolates	15	13	12	17	46	83	165	277	295	140	19	1	1081
Proportion (%)	1.4	1.2	1.1	1.6	4.3	7.7	15.3	25.6	27.3	13.0	1.8	0.1	100.0
Species distribution													
Candida albicans	60.0%	61.5%	50.0%	47.1%	45.7%	45.8%	57.6%	52.0%	53.9%	47.9%	42.1%	-	52.1%
Candida dubliniensis	0.0%	0.0%	8.3%	5.9%	2.2%	3.6%	3.0%	1.4%	1.0%	0.7%	0.0%	-	1.8%
Candida glabrata	6.7%	0.0%	8.3%	23.5%	17.4%	19.3%	25.5%	29.6%	28.8%	37.9%	52.6%	1/1	28.0%
Candida krusei	0.0%	15.4%	8.3%	5.9%	4.3%	10.8%	3.0%	6.1%	3.7%	2.9%	0.0%	-	4.8%
Candida parapsilosis	13.3%	15.4%	8.3%	5.9%	2.2%	4.8%	1.2%	4.3%	6.1%	2.9%	0.0%	-	4.2%
Candida tropicalis	6.7%	0.0%	0.0%	0.0%	13.0%	9.6%	4.2%	2.2%	3.4%	3.6%	5.3%	-	4.1%
Candida species[a]	13.3%	7.7%	0.0%	5.9%	2.2%	4.8%	5.5%	3.6%	1.7%	2.1%	0.0%	-	3.3%
Other fungi[b]	0.0%	0.0%	16.7%	5.9%	13.0%	1.2%	0.0%	0.7%	1.4%	2.1%	0.0%	-	1.8%

[a]*Candida* spp. includes the following species in 2010–11: *C. guilliermondii* 6, *C. inconspicua* 1, *C. kefyr* 6, *C. lambica* 1, *C. lusitaniae* 11, *C. magnolia* 1, *C. norvegensis* 4, *C. orthopsilosis* 2, *C. palmioleophila* 2 and *C. pelliculosa* 2.

[b]Other fungi includes: *Cryptococcus neoformans* 4, *Fusarium oxysporum* 1, *Fusarium proliferatum* 2, *Fusarium solani* 2, *Fusarium* sp. 1, *Geotrichum candidum* 1, *Rhodotorula glutinis* 1, *Saccharomyces boulardii* 1 and *Saccharomyces cerevisiae* 6.

Altta Yatan Hastalıklara Göre Fungemi İnsidansı

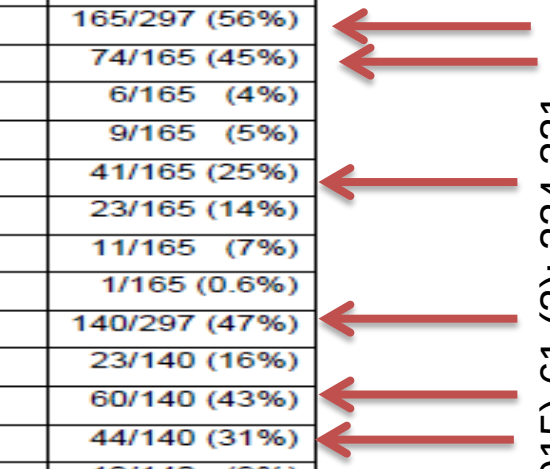
Patient group	Incidence [% (95% CI)]	Patients with fungemia per observed group; N / N
Overall	**0.23% (0.21 – 0.26)**	**333 / 145030**
Solid tumor without HSCT	**0.15% (0.13 – 0.18)**	**174 / 114811**
Gastro-intestinal	0.37% (0.30 – 0.46)	88 / 23718
Lung	0.05% (0.01 – 0.11)	5 / 10976
Breast	0.05% (0.02 – 0.10)	8 / 16137
Genito-urinary	0.20% (0.14 – 0.27)	42 / 21389
Head and Neck	0.13% (0.08 – 0.20)	24 / 18248
Other	0.03% (0.01 – 0.06)	7 / 24343
Solid tumor with HSCT	**1.55% (0.19 – 5.49)**	**2 / 129**
Allogeneic HSCT		1 / 5
Autologous HSCT	0.81% (0.02 – 4.41)	1 / 124
Hematological malignancies without HSCT	**0.42% (0.35 – 0.50)**	**114 / 27195**
ALL	0.64% (0.38 – 1.01)	18 / 2801
AML	0.89% (0.63 – 1.21)	39 / 4403
CLL	0.29% (0.09 – 0.67)	5 / 1738
CML	0.37% (0.04 – 1.32)	2 / 543
MDS	0.57% (0.19 – 1.33)	5 / 875
Lymphoma	0.29% (0.21 – 0.40)	38 / 12933
Multiple myeloma	0.15% (0.05 – 0.35)	5 / 3356
Other	0.37% (0.04 – 1.32)	2 / 546
Hematological malignancies with HSCT	**1.46% (1.06 – 1.97)**	**42 / 2871**
Allogeneic HSCT – related donor	2.10% (1.18 – 3.44)	15 / 715
Allogeneic HSCT – unrelated donor	1.99% (1.00 – 3.54)	11 / 552
Autologous HSCT	1.00% (0.57 – 1.61)	16 / 1604
HSCT without associated malignancies		**1 / 24**



Clin Infect Dis. (2015) 61 (3): 324-331

Kanserli ve Fungemi Gelişen Hastaların Temel Özellikleri (n=297)

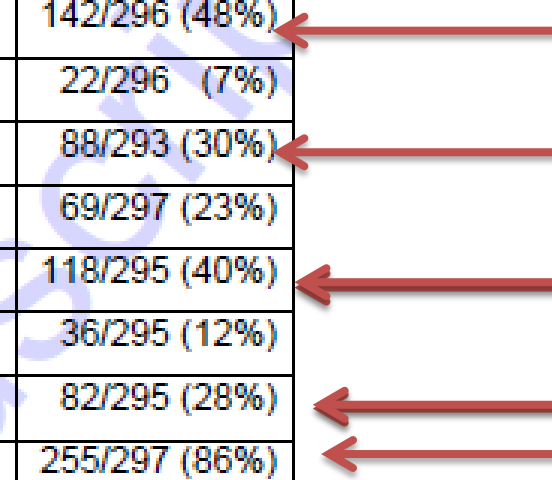
Characteristic	Value N / N
Age, median (min – max)	56 (17 – 88)
Sex, male	153/297 (52%)
Days from hospital admission to diagnosis of fungemia, mean ± std	23 ± 21
Neutropenia <500cells/µl at time of diagnosis of fungemia	110/286 (38%)
Vascular access device upon fungemia diagnosis	280/297 (94%)
Central venous catheter	238/297 (80%)
Peripheral catheter	29/297 (10%)
Both	13/297 (4%)
Underlying disease	
Solid Tumor*	165/297 (56%)
Gastro-intestinal	74/165 (45%)
Lung	6/165 (4%)
Breast	9/165 (5%)
Genito-urinary	41/165 (25%)
Head and neck	23/165 (14%)
Other	11/165 (7%)
Unknown	1/165 (0.6%)
Hematological*	140/297 (47%)
Acute lymphoblastic leukemia	23/140 (16%)
Acute myelogenous leukemia or myelodysplastic syndrome	60/140 (43%)
Lymphoma incl. chronic lymphocytic leukemia	44/140 (31%)
Other	13/140 (9%)
HSCT without associated malignancy	1/297 (0.3%)
Status of malignancy	
Solid Tumor*	
At diagnosis	29/165 (18%)
Complete or partial remission	29/165 (18%)
No change or progressive disease	107/165 (65%)
Hematological malignancy*	
Onset	19/140 (14%)



Clin Infect Dis. (2015) 61 (3): 324-331

Kanserli ve Fungemi Gelişen Hastaların Temel Özellikleri (n=297)

Complete remission	20/140 (14%)
Partial remission, bone marrow hypoplasia, refractory, or relapse	101/140 (72%)
Treatment at fungemia diagnosis	
HSCT	50/297 (17%)
Allogeneic HSCT	28/297 (9%)
Autologous HSCT	22/297 (7%)
Chemotherapy**	142/296 (48%)
Radiation therapy**	22/296 (7%)
Immunosuppressive drugs**	88/293 (30%)
Major surgical procedure**	69/297 (23%)
Total parenteral nutrition**	118/295 (40%)
Stopped prior to fungemia diagnosis	36/295 (12%)
On-going at fungemia diagnosis	82/295 (28%)
Antibiotics**	255/297 (86%)
Antifungals**	89/297 (30%)
Prophylactic	32/297 (11%)
Empiric or curative	57/297 (19%)



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Altta Yatan Hastalıklar, Tedavi grupları ve Kanserli Hastalardaki Kan Kültüründeki Mantarlar

Pathogen isolated by treating center	Total n=297 (%)	Solid tumor[ß] n=165 (%)	Hematological malignancy[ß] n=140 (%)	Allogeneic HSCT n=28 (%)	Autologous HSCT n=22 (%)	No transplant n=247 (%)
Single pathogen	**288 (97.0%)**	**159 (97%)**	**137 (98%)**	**27 (96.4%)**	**22 (100%)**	**239 (96.8%)**
Candida albicans	120 (40.4%)	92 (56%)	31 (22%)	2 (7.1%)	7 (31.8%)	111 (44.9%)
Non-albicans candida	138 (46.5%)	59 (36%)	82 (59%)	21 (75.0%)	12 (54.6%)	105 (42.5%)
C. glabrata	29 (9.8%)	25 (15.2%)	6 (4.3%)	1 (3.6%)	1 (4.5%)	27 (10.9%)
C. tropicalis	39 (13.1%)	11 (6.7%)	30 (21.4%)	2 (7.1%)	4 (18.2%)	33 (13.3%)
C. parapsilosis	28 (9.4%)	16 (9.7%)	11 (7.9%)	5 (17.9%)	2 (9.1%)	21 (8.5%)
C. krusei	25 (8.4%)	5 (3.0%)	20 (14.3%)	6 (21.4%)	4 (18.2%)	15 (6.1%)
C. kefyr	7 (2.4%)	1 (<1%)	6 (4.3%)	2 (7.1%)	1 (4.5%)	4 (1.6%)
C. norvegensis	3 (1.0%)	-	3 (2.1%)	1 (3.6%)	-	2 (0.8%)
C. dubliniensis	2 (<1%)	-	2 (1.4%)	1 (3.6%)	-	1 (0.4%)
C. guilliermondii	2 (<1%)	1 (<1%)	1 (<1%)	1 (3.6%)	-	1 (0.4%)
C. rugosa	1 (<1%)	-	1 (<1%)	-	-	1 (0.4%)
Other Candida*	2 (<1%)	-	2 (1.4%)	2 (7.1%)	-	-
Non-candida yeast**	17 (5.7%)	5 (3%)	13 (9%)	2 (7.1%)	2 (9.1%)	13 (5.3%)
Cryptococcus sp.	4 (1.3%)	1 (<1%)	3 (2%)	-	-	4 (1.6%)
Mold, NOS***	7 (2.4%)	1 (<1%)	7 (5%)	2 (7.1%)	1 (4.6%)	4 (1.6%)
Trichoderma longibrachiatum	2 (<1%)	1 (<1%)	1 (<1%)	-	-	2 (<1%)

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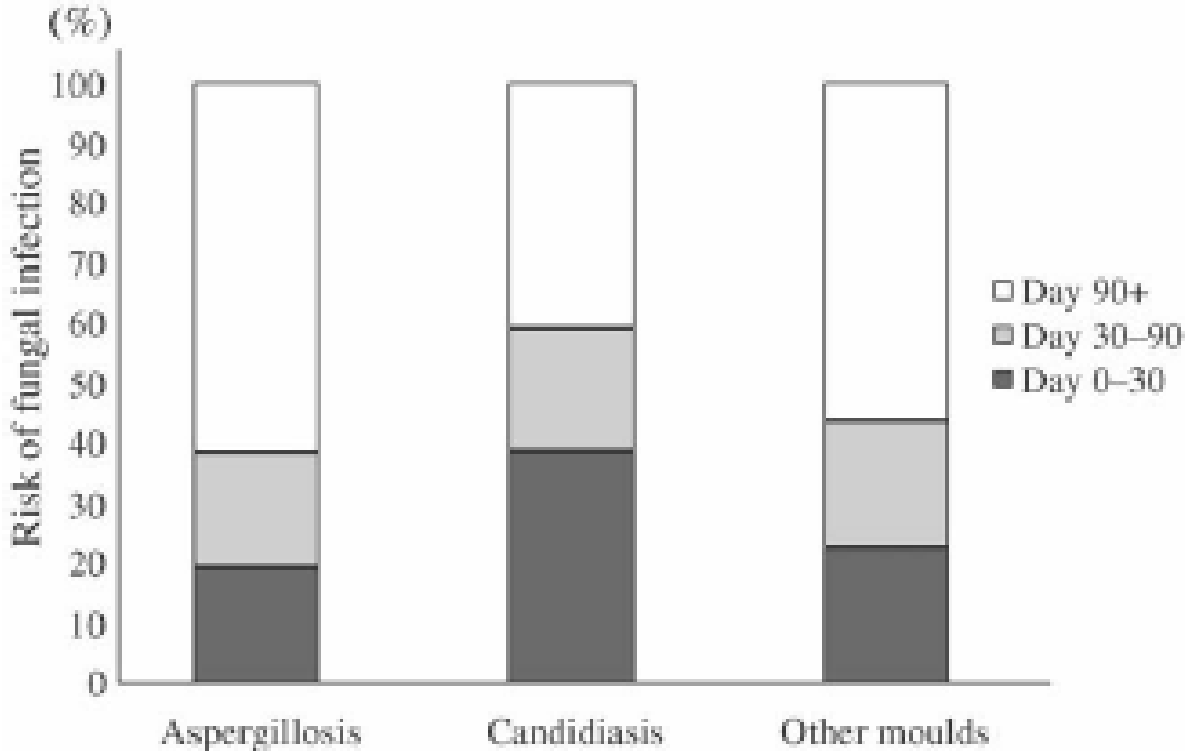

Fig. 2. Timing of invasive fungal infections in allogeneic stem-cell transplant recipients. Reprinted with permission (Warnock David, 2003, personal communication).

International Journal of Antimicrobial Agents 27S (2006) S3–S6

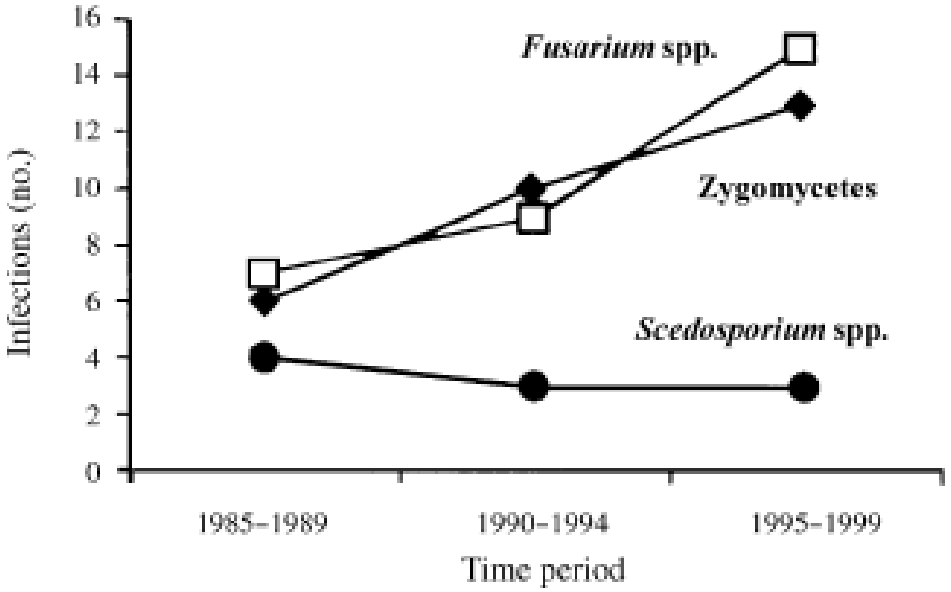

Fig. 1. Number of non-*Aspergillus* mould infections in haematopoietic stem-cell transplant recipients. Reprinted with permission [4]. © 2002 The University of Chicago Press.

International Journal of Antimicrobial Agents 27S (2006) S3–S6

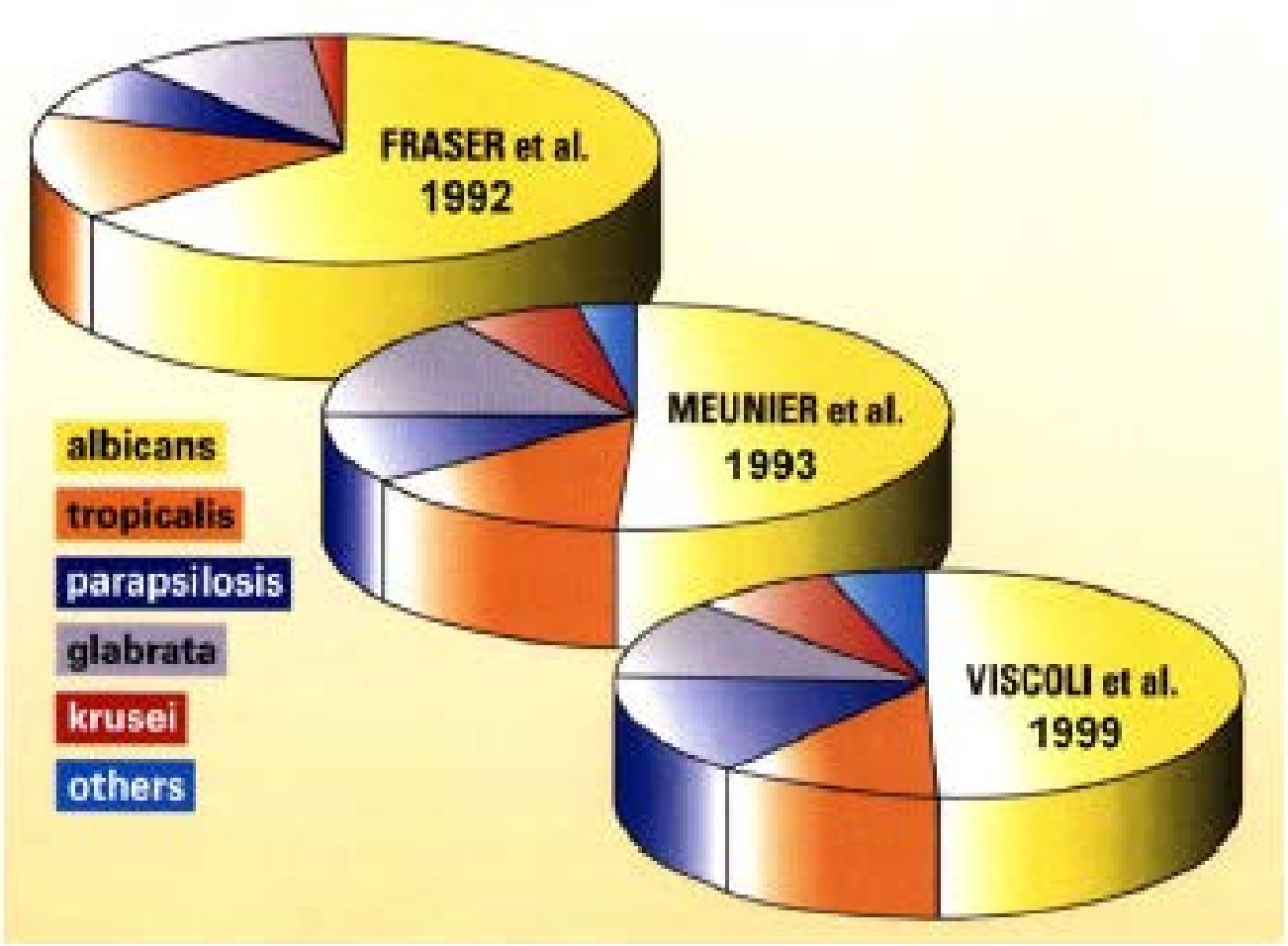

Fig. 4. Changes in predominant infective species in candidaemia [10–12].

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Kullanılan Antifungaller ve Epidemiyoloji

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 532–538 Vol. 55, No. 2
0066-4804/11/$12.00 doi:10.1128/AAC.01128-10

Recent Exposure to Caspofungin or Fluconazole Influences the Epidemiology of Candidemia: a Prospective Multicenter Study Involving 2,441 Patients[▽]

Olivier Lortholary,[1,2,3] Marie Desnos-Ollivier,[1,2] Karine Sitbon,[1,2] Arnaud Fontanet,[4] Stéphane Bretagne,[1,2,5] Françoise Dromer,[1,2*] and the French Mycosis Study Group†

Institut Pasteur, Unité de Mycologie Moléculaire, Centre National de Référence Mycologie et Antifongiques, Paris,[1] CNRS URA3012, Paris,[2] Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, Hôpital Necker-Enfants Malades, APHP, Paris,[3] Institut Pasteur, Unité d'Epidémiologie des Maladies Emergentes, Paris,[4] and Laboratoire de Parasitologie-Mycologie, Université Paris-Est, and Hôpital Henri Mondor, AP-HP, Créteil,[5] France

Received 15 August 2010/Returned for modification 20 September 2010/Accepted 29 October 2010

A prospective multicenter surveillance program on yeast bloodstream infections was implemented in the Paris, France, area without restrictions on ward of hospitalization (intensive care unit, hematology, and surgery) or age (adults and children). The present analysis concerns 2,618 isolates collected over 7 years from 2,441 patients. Centralized species identification and antifungal susceptibility testing using the EUCAST methodology were performed. Almost 10% (232/2,441) of the patients had recently (≤30 days) been treated with antifungal drugs. We analyzed the effect of recent exposure to fluconazole ($n = 159$) or caspofungin ($n = 61$) on the proportions of the five major *Candida* species. For both drugs, preexposure was associated with a decreased prevalence of *Candida albicans* in favor of less drug-susceptible species (*C. glabrata* and *C. krusei* for the former and *C. parapsilosis* and, to a lesser extent, *C. glabrata* and *C. krusei* for the latter; $P = 0.001$). In the multivariate analysis, the risk of being infected with an isolate with decreased susceptibility to fluconazole was independently associated with an age of ≥15 years (odds ratio [OR] = 2.45; 95% confidence interval [CI] = 1.39 to 4.31; $P = 0.002$) and with recent exposure to fluconazole (OR = 2.17; 95% CI = 1.51 to 3.13; $P < 0.001$), while the risk of being infected with an isolate with decreased susceptibility to caspofungin was independently associated with an age <15 years (OR = 2.53; 95% CI = 1.43 to 4.48; $P = 0.001$) and with recent exposure to caspofungin (OR = 4.79; 95% CI = 2.47 to 9.28; $P < 0.001$). These findings could influence future recommendations for the management of candidemia.

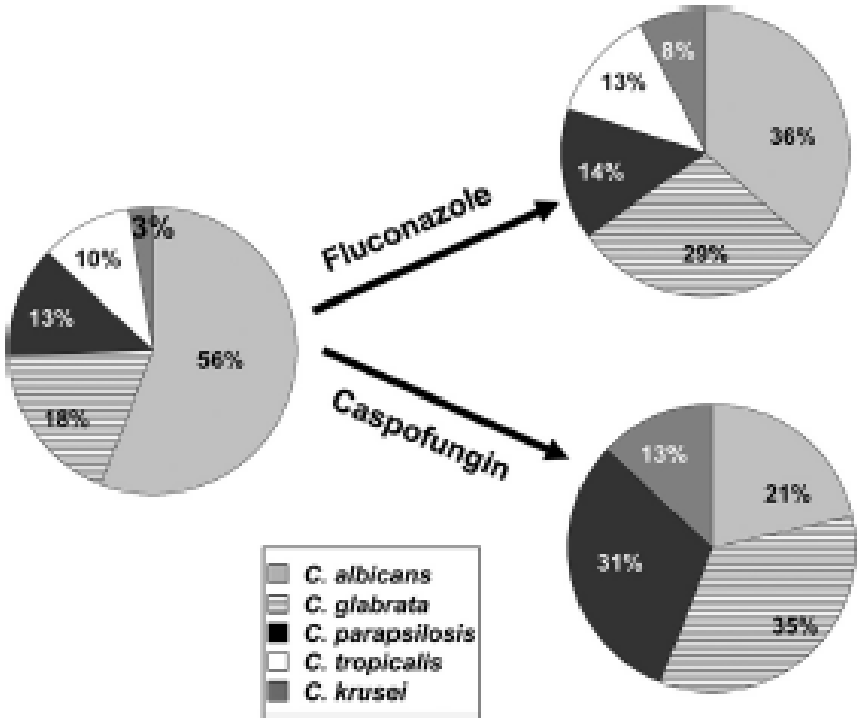

FIG. 2. Proportion of the five major *Candida* species responsible for fungemia in patients with ($n = 159$) or without ($n = 2,289$) prior exposure to fluconazole ($P = 0.001$) or with ($n = 61$) or without ($n = 2,387$) prior exposure to caspofungin ($P < 0.001$) (incident episodes and recurrences are included).

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 532–538

TABLE 1. Antifungal susceptibility of the five most frequent *Candida* species responsible for bloodstream infections according to recent exposure to fluconazole or caspofungin prior to diagnosis of fungemia[a]

Exposure drug and antifungal	No preexposure recorded		Preexposure recorded		P^b
	No. of isolates	GMIC (mg/liter)	No. of isolates	GMIC (mg/liter)	
Fluconazole					
Total	2,289	0.77 (0.71–0.83)[c]	159	2.31 (1.65–3.23)	<0.001
C. albicans	1291	0.24 (0.23–0.24)	58	0.36 (0.25–0.51)	0.053
C. glabrata	413	13.97 (12.59–15.50)	46	18.05 (13.19–24.70)	0.129
C. parapsilosis	295	0.97 (0.86–1.08)	23	1.62 (0.99–2.64)	0.015
C. tropicalis	226	0.84 (0.70–1.00)	20	1.52 (0.76–3.01)	0.040
C. krusei	64	34.15 (29.88–39.02)	12	28.51 (10.78–75.41)	0.402
Caspofungin					
Total	1920	0.07 (0.07–0.08)	61	0.16 (0.12–0.22)	<0.001
C. albicans	993	0.05 (0.05–0.05)	13	0.09 (0.04–0.22)	0.252
C. glabrata	365	0.07 (0.07–0.08)	21	0.12 (0.08–0.19)	0.418
C. parapsilosis	299	0.28 (0.26–0.31)	19	0.32 (0.23–0.45)	0.893
C. tropicalis	199	0.06 (0.05–0.06)	0		
C. krusei	64	0.15 (0.13–0.17)	8	0.19 (0.11–0.33)	0.571

[a] Recent exposure was <30 days prior to diagnosis of fungemia, and data for incident episodes and first recurrences are included. GMIC, geometric mean MIC.
[b] Mann-Whitney test.
[c] Values in parentheses are 95% CIs.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 532–538

TABLE 2. Characteristics of patients and *Candida* sp. isolates responsible for incident fungemia according to recorded or not recorded recent exposure[d] to fluconazole or caspofungin

Group and characteristic	Recent exposure to fluconazole			Recent exposure to caspofungin		
	None recorded (n = 2,305)	Recorded (n = 136)	P	None recorded (n = 2,391)	Recorded (n = 50)	P
Patients						
Mean age (yr)	56.9 (56.1–57.8)[c]	50.7 (47.0–54.5)	<0.001	56.9 (56.0–57.7)	42.7 (36.7–48.6)	<0.001
Male gender[a]	1,392/2,305 (60.4)	78/136 (57.4)	0.528	1,435/2,391 (60.0)	35/50 (70.0)	0.189
Hematological malignancy[a]	411/2,305 (17.8)	31/136 (22.8)	0.168	414/2,391 (17.3)	28/50 (56.0)	<0.001
Intensive care unit[a]	1,073/2,305 (46.6)	80/136 (58.8)	0.006	1,133/2,391 (47.4)	20/50 (40.0)	0.320
Central venous catheter[a]	1,723/2,305 (74.8)	115/136 (84.6)	0.010	1,793/2,391 (75.0)	45/50 (90.0)	0.012
After diagnosis of fungemia, prescription of[a]:						
Fluconazole	1,233/1,938 (63.6)	43/129 (33.3)	<0.001	1,269/2,022 (62.8)	7/45 (15.6)	<0.001
Caspofungin	393/1,938 (20.3)	52/129 (40.3)	<0.001	424/2,022 (21.0)	21/45 (46.7)	<0.001
Death before day 30[a]	859/2,185 (39.3)	54/134 (40.3)	0.856	892/2,271 (39.3)	21/48 (43.8)	0.552
Early death (<day 8)[a]	481/846 (56.9)	26/53 (49.1)	0.318	497/878 (56.6)	10/21 (47.6)	0.506
Isolates[b]						
Mixed infection[a]	75/2,305 (3.3)	3/136 (2.2)	0.800	77/2,391 (3.2)	1/50 (2.0)	1.000
Non-*C. albicans* species[a]	1,107/2,377 (46.6)	89/139 (64.0)	<0.001	1,157/2,465 (46.9)	39/51 (76.5)	<0.001
C. glabrata isolates[a]	393/2,377 (16.5)	35/139 (25.2)	0.011	413/2,465 (16.8)	15/51 (29.4)	0.023
Geometric mean MIC (mg/liter) for the isolate causing fungemia						
Fluconazole	0.77 (0.71–0.83)[c]	2.14 (1.51–3.04)	<0.001	0.80 (0.74–0.86)	2.17 (1.23–3.82)	<0.001
Caspofungin	0.07 (0.07–0.08)[c]	0.08 (0.07–0.09)	0.199	0.07 (0.07–0.07)	0.17 (0.13–0.23)	<0.001
Episodes due to at least one isolate with decreased susceptibility to[a]:						
Fluconazole	452/2,305 (19.6)	47/136 (34.6)	<0.001	480/2,391 (20.1)	19/50 (38.0)	0.004
Caspofungin	121/1,854 (6.5)	10/106 (9.4)	0.231	119/1,910 (6.2)	12/51 (24.0)	<0.001

[a] The data indicate the number of individuals or isolates for whom the corresponding information was available/total number in the group (%).
[b] The total number of isolates studied during incident candidemia was 2,516.
[c] Values in parentheses in this row are 95% CIs.
[d] Recent exposure was <30 days prior to diagnosis of fungemia.

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Emergence of fusarioses in a university hospital in Turkey during a 20-year period

B. Dalyan Cilo[1] · A. M. S. Al-Hatmi[2,3,4] · S. Seyedmousavi[10,11,12] · A. J. M. M. Rijs[10] · P. E. Verweij[10] · B. Ener[1] · G. S. de Hoog[2,3,5,6,7,8,9] · A. D. van Diepeningen[3]

Cilo BD, Eur J Clin Microbiol Infect Dis 2015

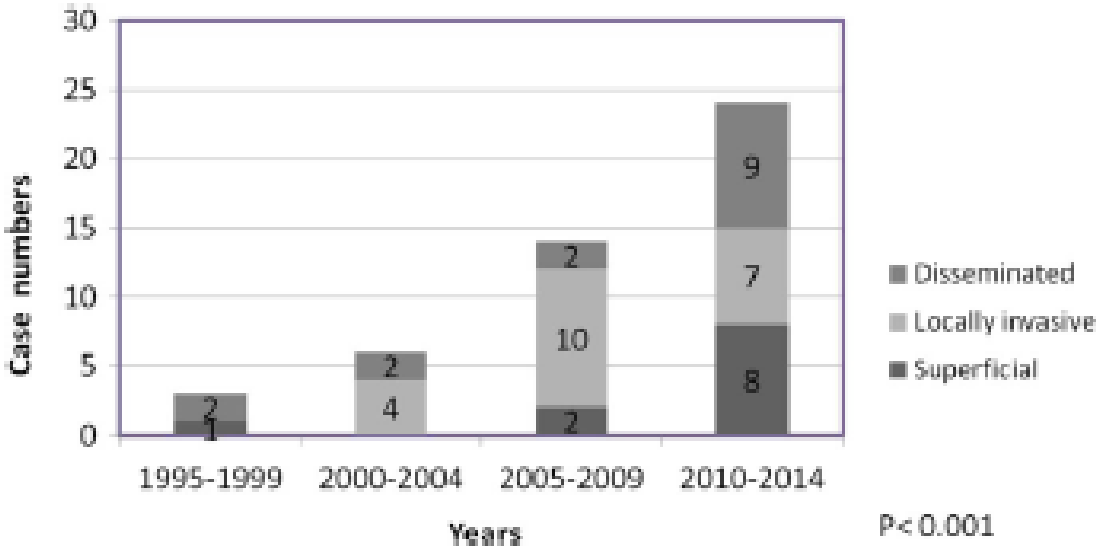


Fig. 1 Increasing incidence of *Fusarium* infections over the past 20 years in the studied university hospital in Turkey

Cilo BD, Eur J Clin Microbiol Infect Dis 2015

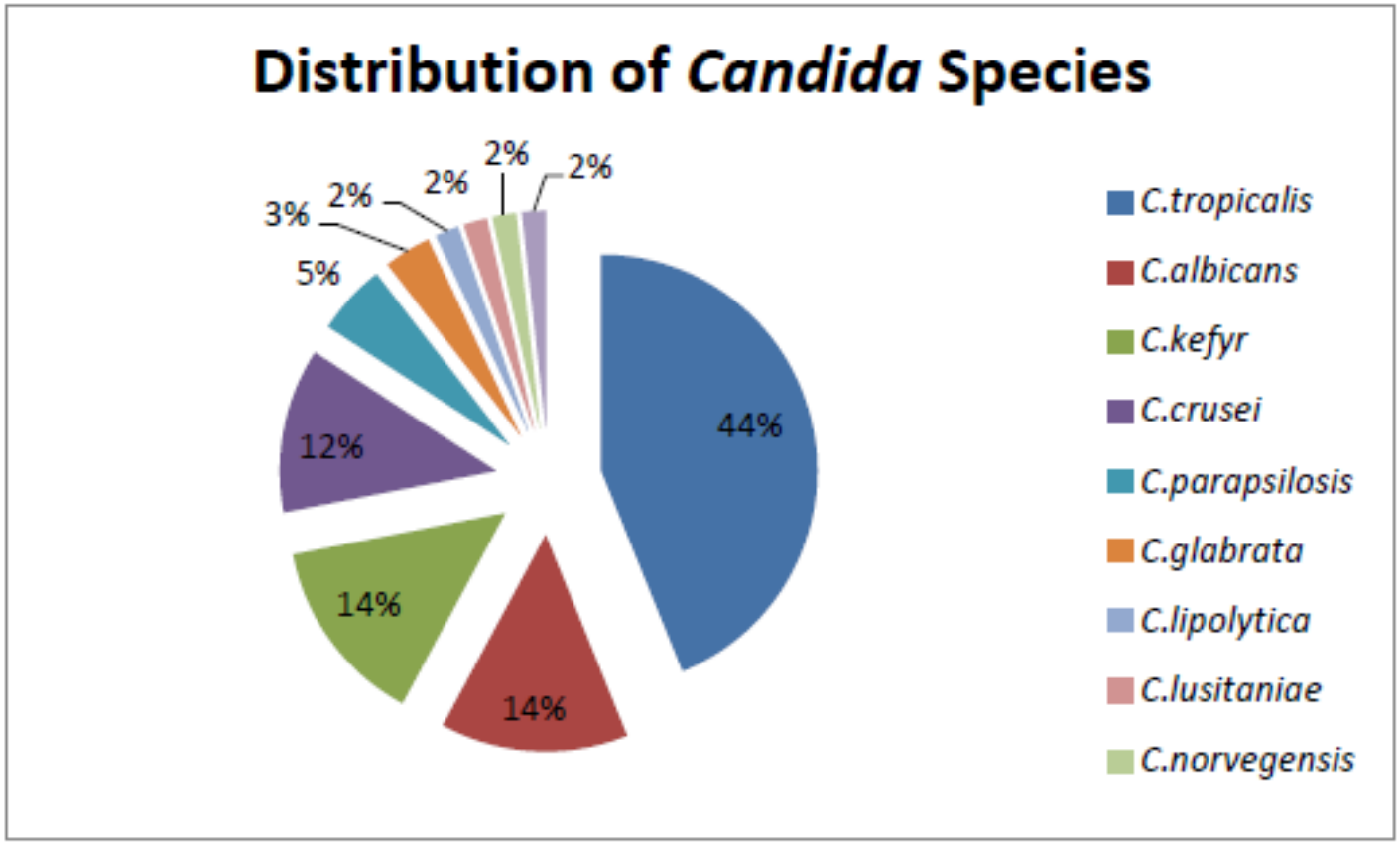
Evaluation of candidemia episodes in patients with hematological malignancy between January 2006 and December 2013

Gülden YILMAZ[1], Ayşe ÇİFTÇİoğlu[2], Mehmet GÜNDÜZ[2], Mehmet ÖZEN[2], Hamdi AKAN[2]

[1]: Ankara University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology

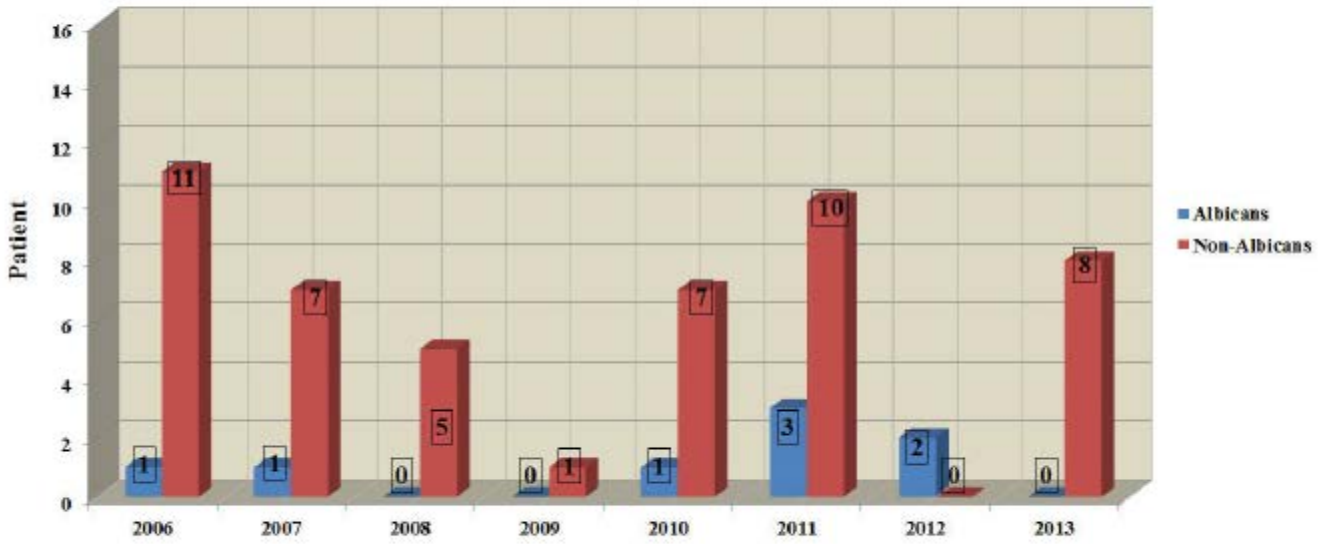
[2]: Ankara University, Faculty of Medicine, Department of Hematology.

TJMS 2015


Distribution of *Candida* Species
44%
14%
14%
12%
5%
3%
2%
2%
2%
2%
C.tropicalis
C.albicans
C.kefyr
C.crusei
C.parapsilosis
C.glabrata
C.lipolytica
C.lusitaniae
C.norvegensis

TJMS 2015

Figure 2: Distribution of Candidemia Cases by Year



TJMS 2015

Antifungal Direnç

Microbiyolojik Direnç
İnvitro bir antifungal ajana karşı mantarların duyarlı olmaması

Belirlenen organizmaya yönelik duyarlık MİK değerinin üzerine çıkması

Klinik Direnç

İnfeksiyon etkeni olan patojene yönelik invitro aktivitesi olan antifungallerin uygulanmasına rağmen fungal infeksiyonun eradike edilememesidir.

Kombine

Antifungal Direnç

BMD (Broth Microdilution): Maya ve Küf

-CLSI

-EUCAST

Disk Difüzyon (DD): Maya ve Küf

-CLSI

Değişik ticari ürünler

-E-Test

-Vitek2

-Sensititre YeastOne

Antifungallerde Direnç Durumu

Candida krusei	Flukonazol	İntrinsik
Candida glabrata	Flukonazol	Edinsel
	Kaspofungin	
Candida albicans	Flukonazole	Edinsel
	Kaspofungin	
Candida lusitanae	Amfoterisin B	
Aspergillus terreus	Amfoterisin B	İntrinsik
Pseudallescheria boydii	Amfoterisin B	
Paecilomyces lilanicus	Amfoterisin B	
Fusarium species	Tümü	

Mantarlar ile In Vitro/In Vivo Doğrulamasıyla Yüzleşme

Aspergillus terreus	Amfoterisin B	Intrinsik
Candida glabrata	Azol	Intrinsik ve edinsel
Candida krusei	Azol	Intrinsik
Candida lusitaniae	Amfoterisin B	Intrinsik ve edinsel
Histoplasma capsulatum	Flukonazol	Edinsel

Pfaller, Rex 2002

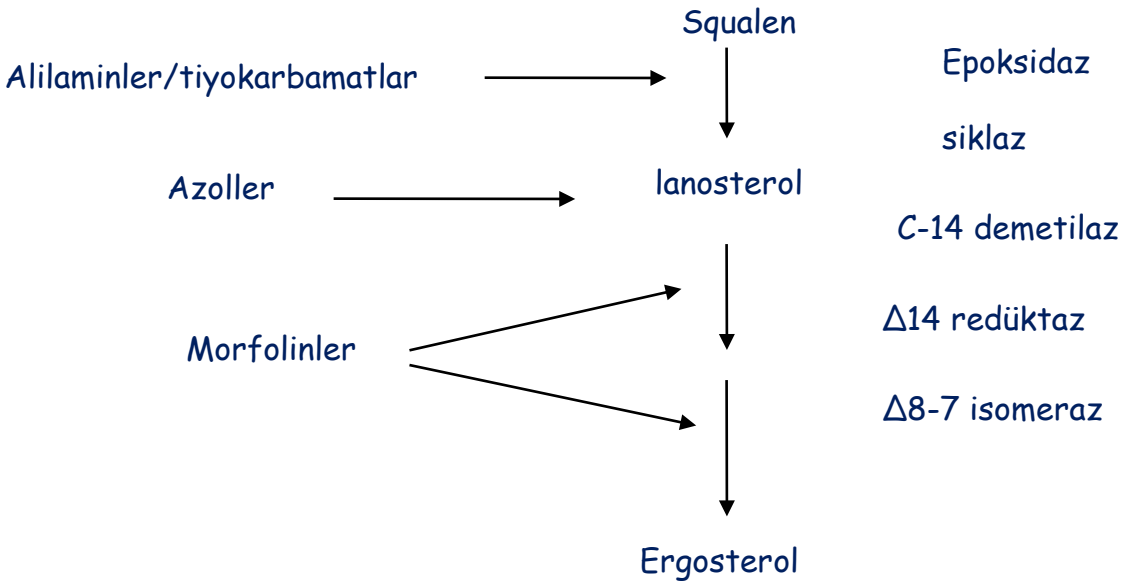
Kandidemi Etkenleri ve Duyarlılıkları

Candida species	Source	Predisposing factor(s)	Susceptibility to antifungal agents			
			Fluconazole	Itraconazole	Flucytosine	Amphotericin B
C. albicans	Endogenous (gastrointestinal tract), exogenous	Neutropenia, mucosal damage, presence of vascular catheter	S	S	S to R[a]	S
C. glabrata	Endogenous	Solid tumor, abdominal surgery, prior use of azoles	S-DD to R	S-DD to R	S	S to I
C. parapsilosis	Exogenous, endogenous	Presence of vascular catheter, hyperalimentation, presence of prosthetic heart valve	S	S	S	S
C. tropicalis	Endogenous	Neutropenia, mucosal damage	S	S	S	S
C. krusei	Endogenous	Neutropenia, receipt of fluconazole prophylaxis	R	S-DD to R	I to R	S to I
C. lusitaniae	Endogenous, exogenous	Neutropenia, hematologic malignancy	S	S	S	S to R
C. guilliermondii	Endogenous	Neutropenia	S	S		S to R
C. dubliniensis	Endogenous	Neutropenia, mucosal damage, HIV infection	S	S	S	S

Seçilmiş İlaca Dirençli Mantarların Antifungallere Duyarlıkları

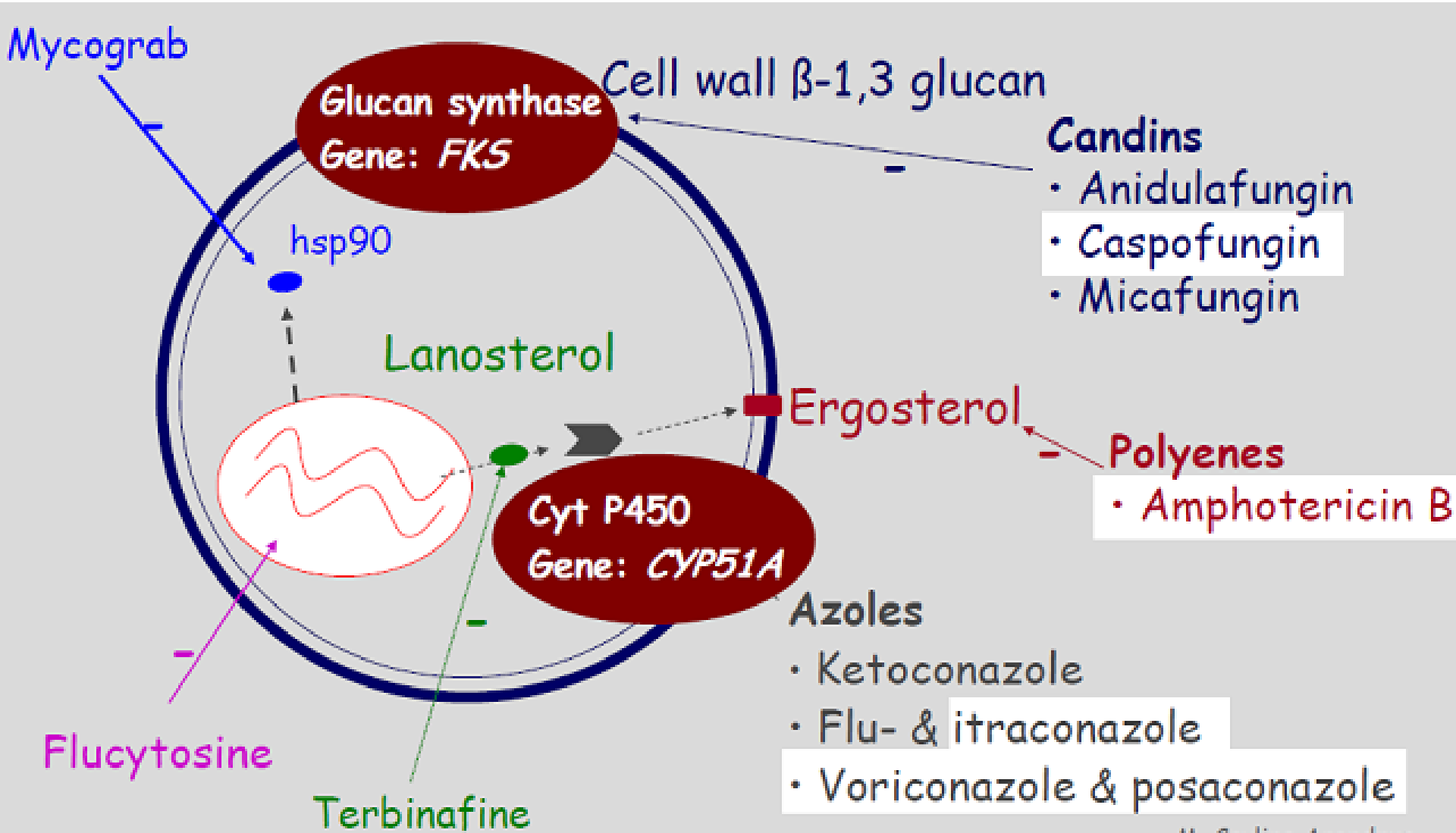
Species	MIC range, mg/mL (no. of isolates)				CAS, minimal effective concentration range in mg/mL (no. of isolates)
	ICZ	VCZ	PCZ	AMB	
Aspergillus lentulus	0.5–1 (8)	1–2 (8)	NA	1–2 (8)	2–16 (8)
Aspergillus ustus	1 to >8 (10)	4–8 (10)	2 (1)	0.25–8 (10)	2–8 (8)
Aspergillus terreus	0.03–8 (63)	0.25–4 (63)	0.06–0.25 (8)	0.12–16 (63)	0.06–0.5 (13)
Scedosporium apiospermum	0.03–2 (30)	≤0.03 to 0.5 (30)	0.125–1 (13)	0.5 to >16 (30)	0.25–4 (11)
Scedosporium prolificans	2 to >32 (55)	0.5–8 (55)	2 to >8 (55)	1 to >16 (55)	4–8 (2)
Fusarium solani	≥8 (15)	1–4 (10)	>8 (6)	0.25–8 (15)	≥8 (29)
Paecilomyces lilacinus	1 to >8 (3)	0.2–1 (3)	0.12–0.5 (3)	>8 (3)	3 to >100 (5)
Scopulariopsis brevicaulis	>8 (25)	>8 (25)	>8 (25)	8 to >16 (25)	4 to >16 (25)
Zygomycetes	0.03–32 (51)	2–64 (51)	0.06–2 (36)	0.03–2 (51)	>16 (15)
Trichosporon asahii	0.03–8 (15)	0.015–8 (15)	0.12–1 (5)	0.5–16 (15)	>16 (9)
Geotrichum capitatum	0.03–0.5 (23)	0.03–0.5 (23)	NA	0.06–0.25 (23)	0.5 (1)
Cladophialophora bantiana	≤0.03 to 0.25 (10)	≤0.03 to 1 (10)	<0.03 to 0.06 (5)	0.25–0.5 (10)	2–8 (5)

GENEL ETKİ MEKANİZMALRI



Ergosterol biyosentez basamakları ve antifungal ilaçların etki yerleri

Antifungaller ve Etki Mekanizmaları

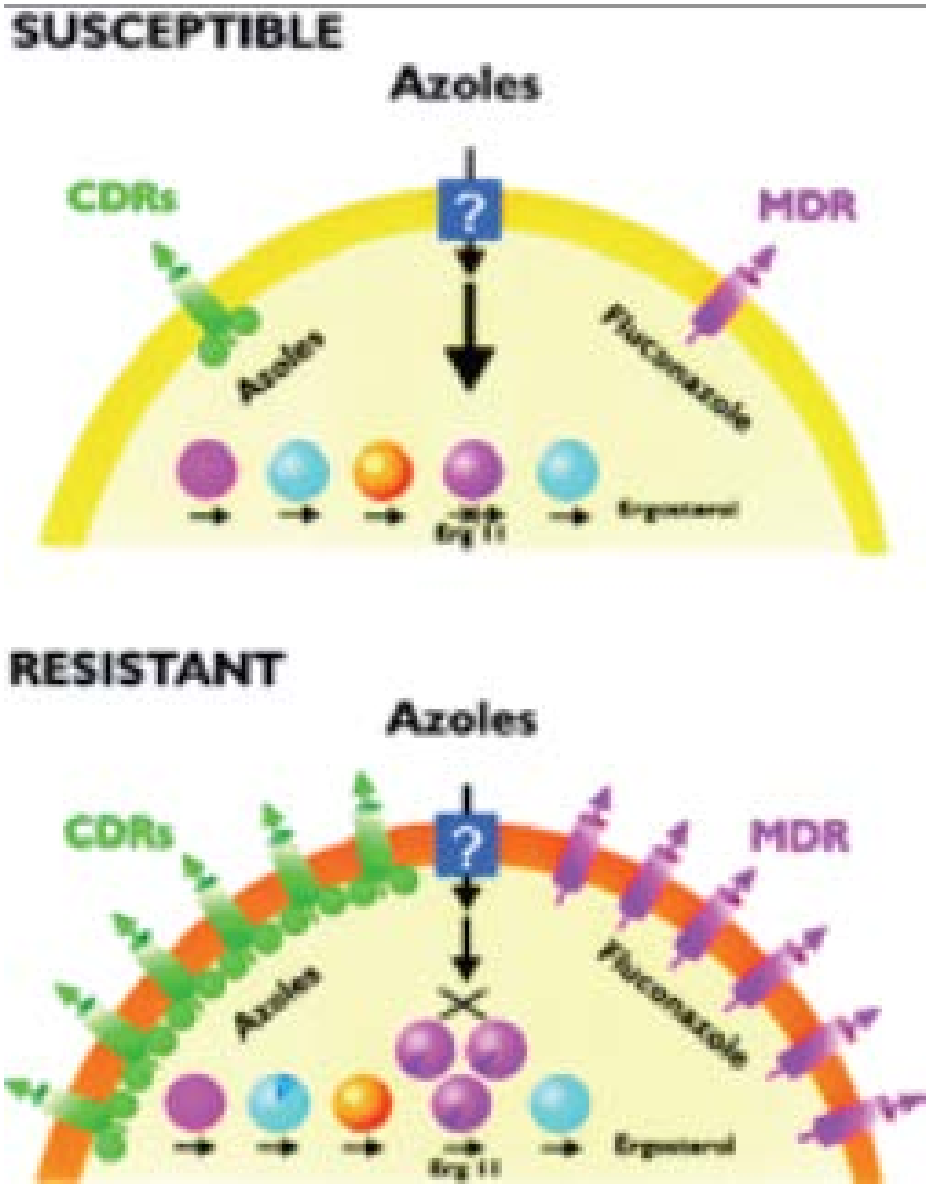


Antifungal Dirençler: Direnç Mekanizmaları

- ✓ Azol
  - ✓ Hedef değişimi/amplifikasyonu
  - ✓ Effluks
- ✓ Ekinokandinler
  - ✓ Hedef değişimi

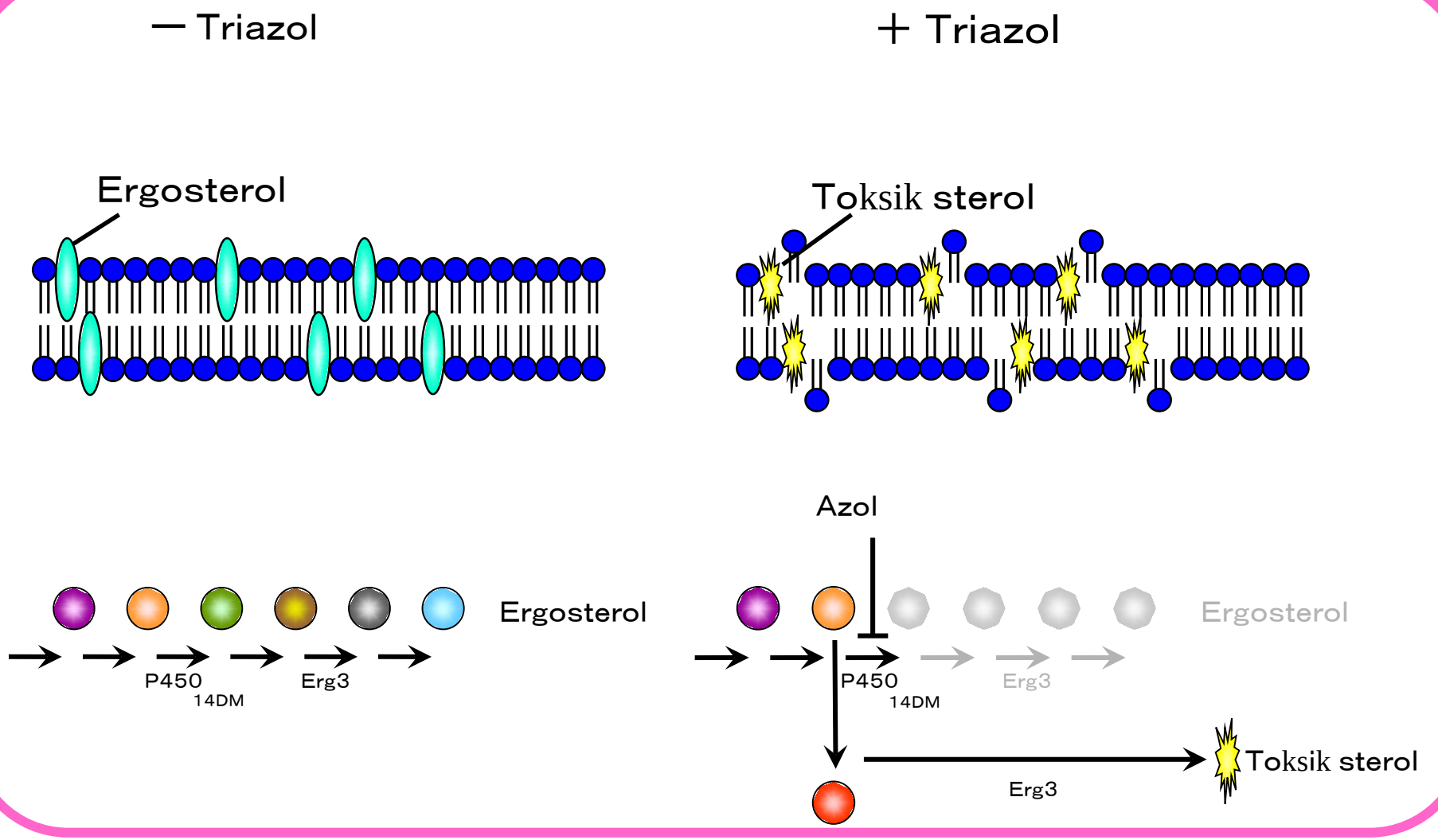
Table 2: Nature, target, mode of action, and fungal resistance mechanisms of the major antifungal drugs used in human therapy.

Antifungal agent	Mode of action and cellular target	Mechanism of resistance
polyenes	binding to ergosterol	absence of ergosterol (loss of function mutation in *ERG3* or *ERG6*) decrease of ergosterol content in cells
azoles	inhibition of cytochrome p450 function: 14α-lanosterol demethylase (*ERG11*) sterol Δ^{22} desaturase (*ERG5*)	efflux mediated by multidrug transporters decrease of affinity in Erg11p by mutations upregulation of *ERG11* alterations in the ergosterol biosynthetic pathway
allylamines	inhibition of squalene epoxidase (*ERG1*)	unknown
morpholines	inhibition of sterol Δ^{14} reductase (*ERG24*) and the Δ^{7-8} isomerase (*ERG2*)	unknown
5-fluorocytosine	inhibition of nucleic acids synthesis	defect in cytosine permease deficiency or lack of enzymes implicated in the metabolism of 5-FC deregulation of the pyrimidine biosynthetic pathway
echinocandins	inhibition of β-1,3 glucan synthase (*FKS1&2*)	alteration of affinity of echinocandins for β(1,3)-glucan synthase



Clin Microbiol Rev 1998;11:382-402.

Azollerin Etki Mekanizmaları



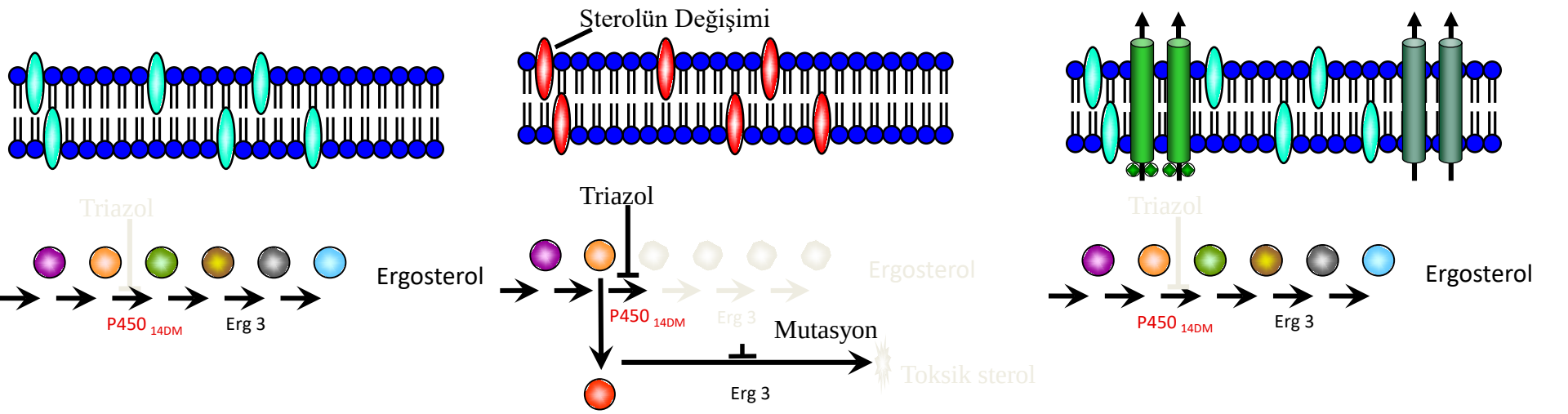
Cowen LE. *Eukaryotic Cell* 2008 7:747-764

Azollere Direnç Mekanizmaları

aP450$_{14DM}$ geninde değişiklik, mutasyon ve aşırı işlenmesi

Erg3 Mutasyonu ve sentez değişikliği

Effluks pompasının aşırı işlenmesi



Cowen LE. *Eukaryotic Cell* 2008 7:747-764

Tanımlamalar: Azole-Dirençli

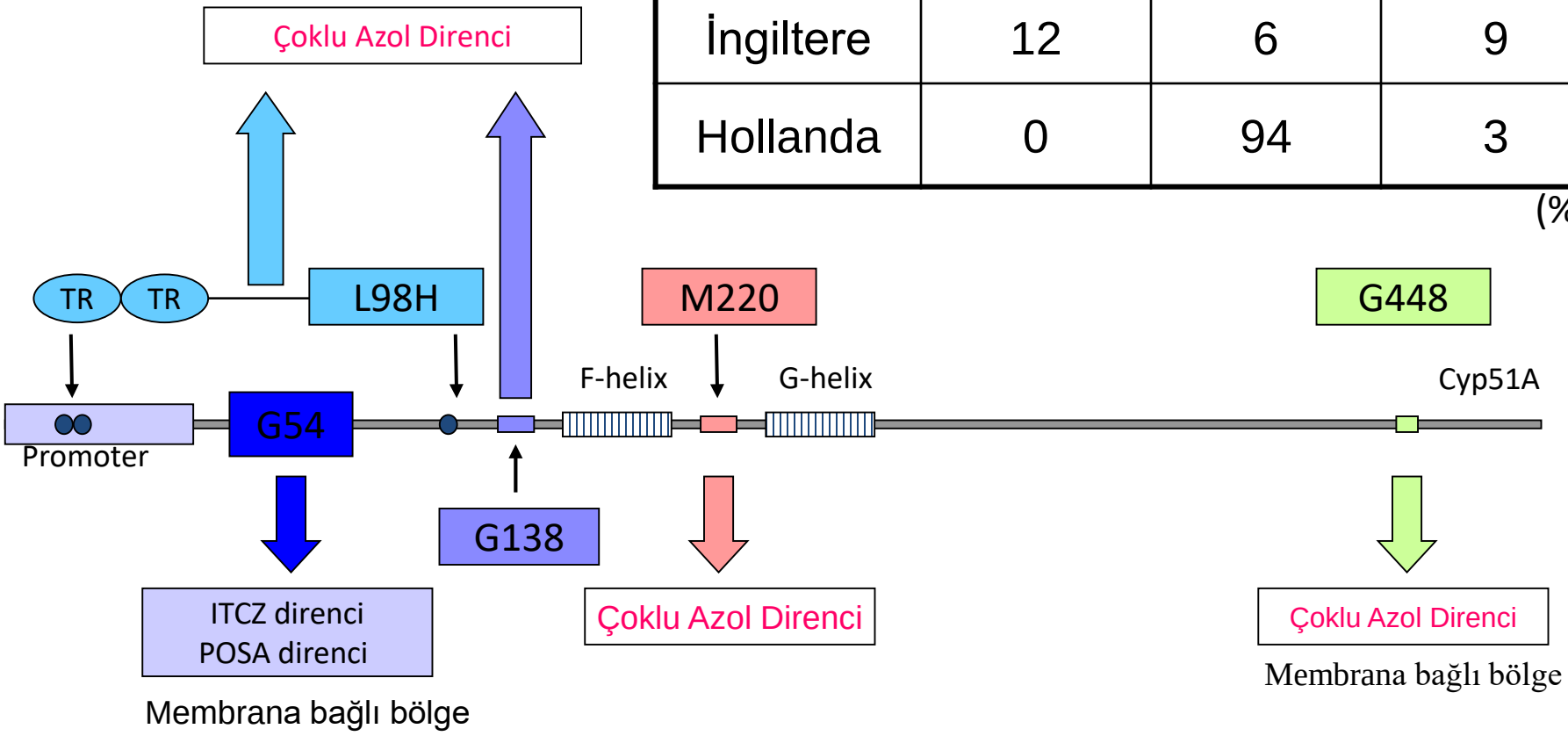
1. Azol: Tek ilaç direnci (ITC ve VOR > 4µg/ml, POS > 2µg/ml)
2. Çoklu azol direnci: En az 2 veya üzerinde ilaca direnç olması
3. Panazol: Tüm test edilen azollere karşı direnç olması

Denning, Verweij, 2009

A. fumigatus'de Azol Direnci Mekanizması; Cyp51A mutasyonu

	G54	TR+L98H	M220
İngiltere	12	6	9
Hollanda	0	94	3

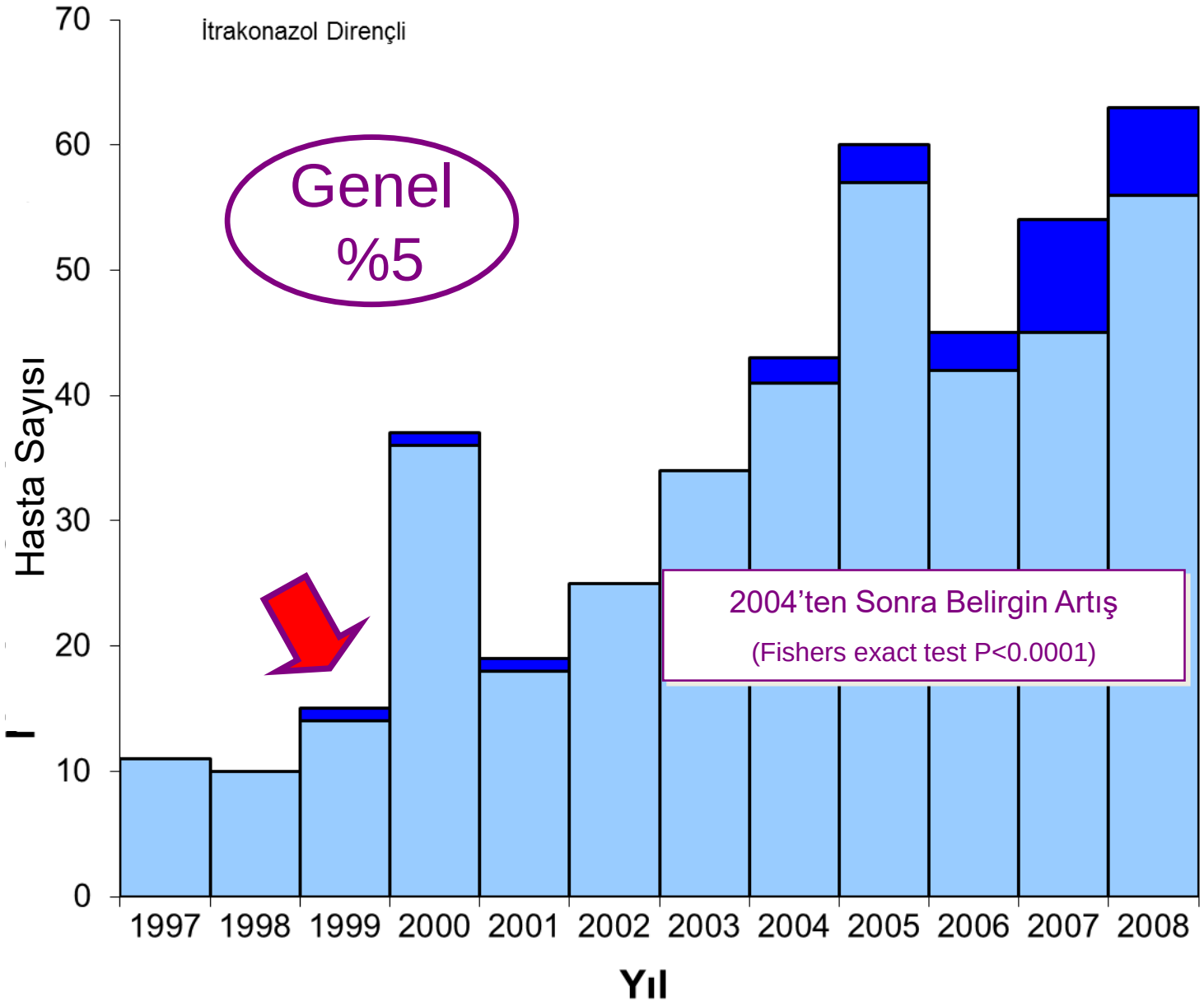
(%)



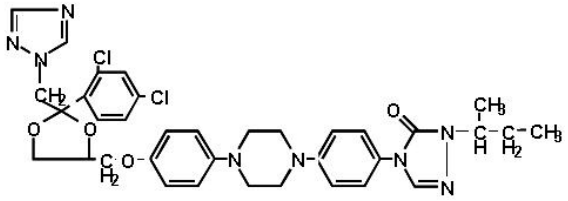
Verweij PE, et al. Lancet Infect Dis 9: 789-795, 2009

Aspergillus fumigatus'un İlaç Duyarlılığı-Nagasaki Universite Hastanesinde Klinik İzolatlar (196 izolat) (Wild-type dışı sıklığı) Avrupa Verileri ile Cyp51 A Mutasyon Hızı İçin Karşılaştırma

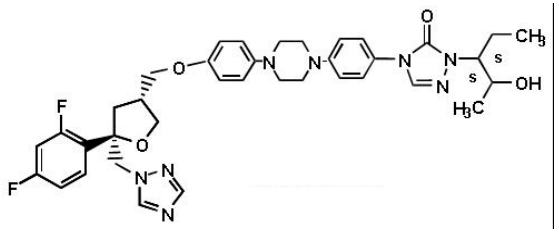
	Cyp51 A Mutasyon Hızı
Nagasaki, JAPAN	% 87.5
U.K.	% 57
Netherland	% 88


İtrakonazol Dirençli
Genel
%5
Hasta Sayısı
70
60
50
40
30
20
10
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Yıl
2004'ten Sonra Belirgin Artış
(Fishers exact test P<0.0001)

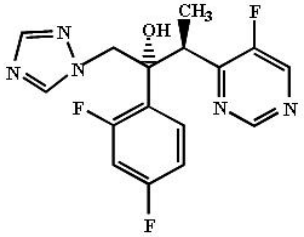
Azol Çapraz Direnci



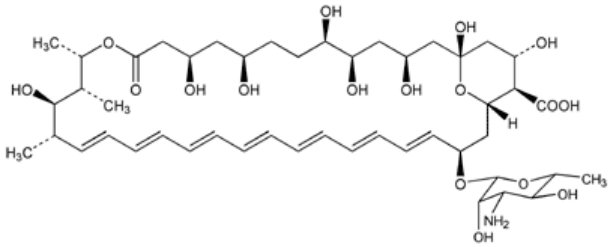
Itra direnci = % 100



Posa direnci = % 74



Vori direnci = %65



Amf-B direnci = % 0

Howard SJ *et al*. *EID*. 2009;15:1068-76

Çapraz Direnç

- ✓ Çapraz direnç azol ilaçları arasında in vivo ve in vitro olarak gerçekleşir ve Cyp51A'de özgün mutasyonlara bağlı olarak gelişir.
- ✓ ITC ve posakonazol arasında bildirilmiştir.
- ✓ ITC ve vorikonazol arasında bildirilmemiştir.

Oakley 2000, Moore 2000

Çoğul Triazol Dirençli Aspergilloz

Verweij PE, Mellado E, Melchers WJ

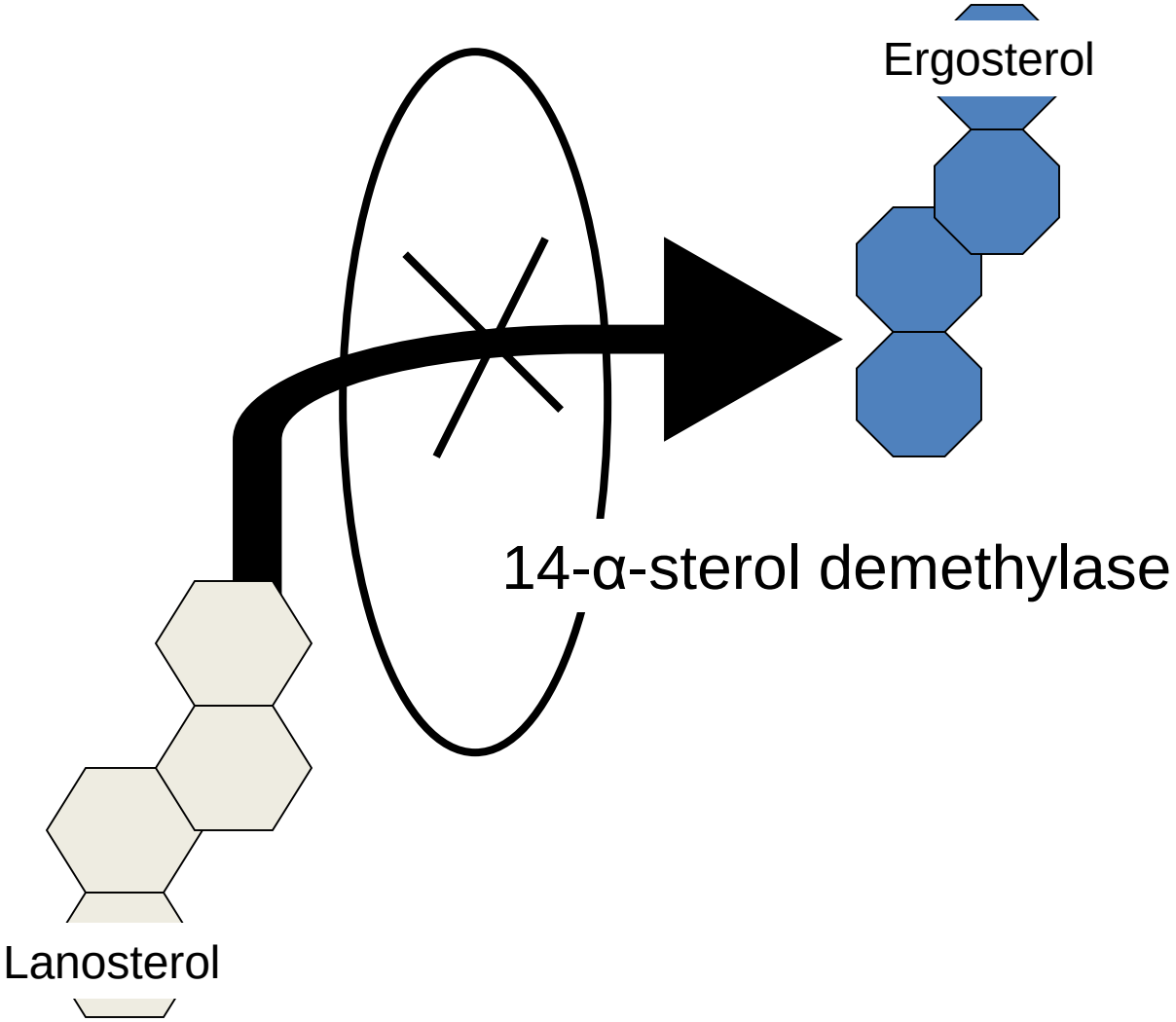
N Engl J Med. 2007 356 (14):1481-3.

Klinik Özellikler	
Primer Direnç	+
Sekonder Direnç	++
In vivo-in vitro Doğrulama	++
Risk faktörleri	Uzun süreli azol tedavisi: ++ Uzun sureli azol profilaksisi: ++
Çağraz Direnç	++
Çoklu Azol Direnci	++
Sonuçlar	Ölüm: ++

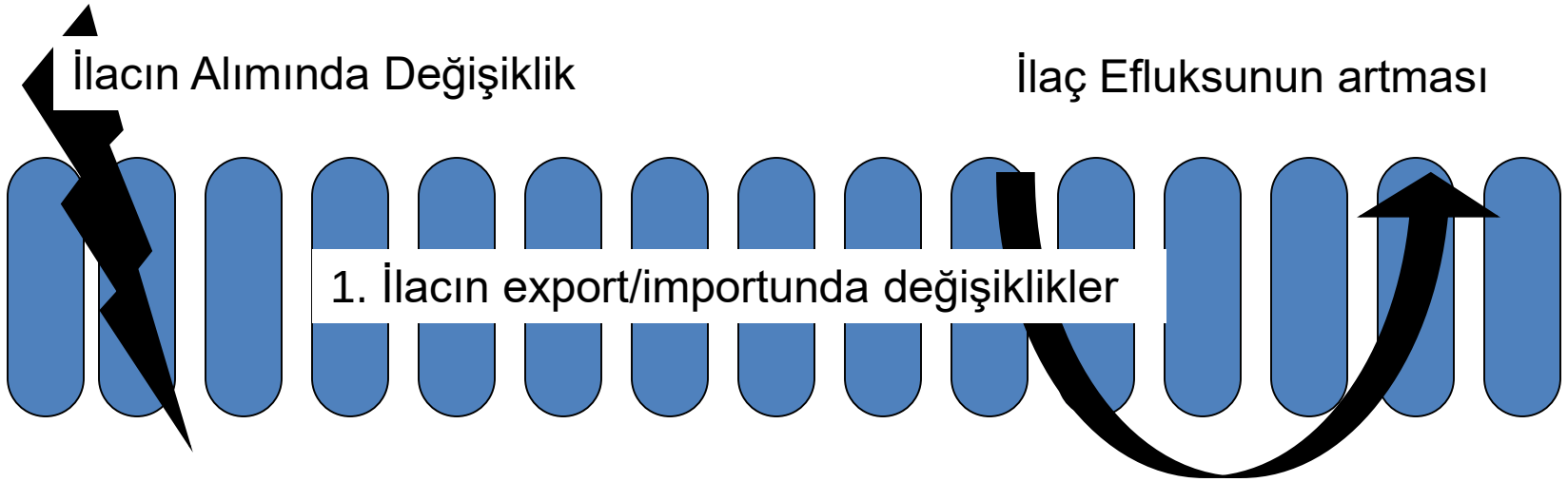
(+)'lar ağırlığı gösterir

Lass-Flörl, 2009

Azoller: Vorikonazol, Posakonazol, Itrakonazol

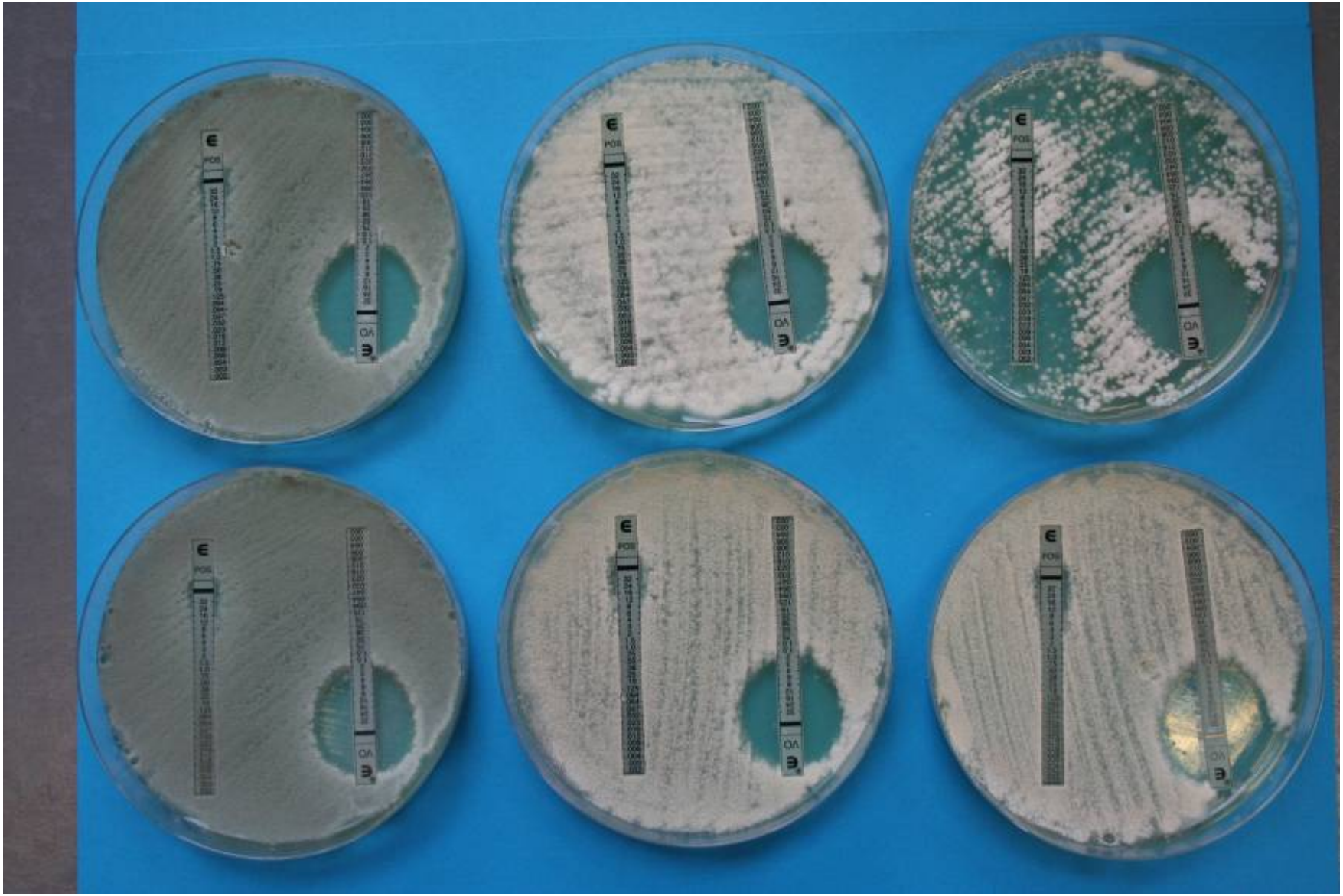


Azollere Karşı Direnç Mekanizması



*Ccyp*51A geninde mutasyon

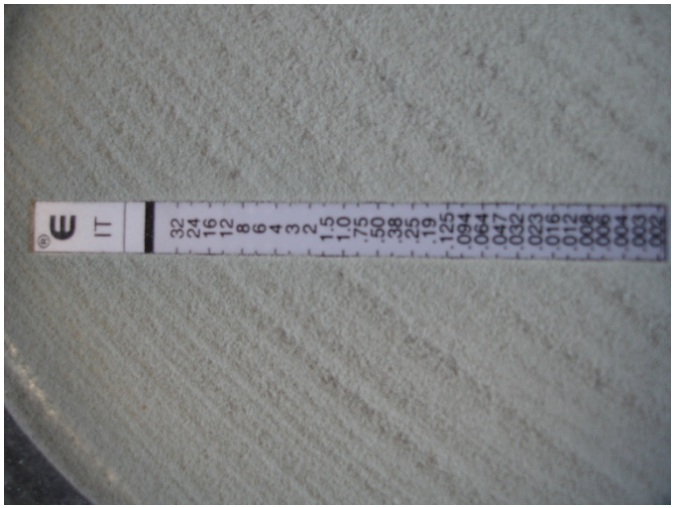
AZOLE DİRENÇLİ ASPERGILLUS FUMIGATUS



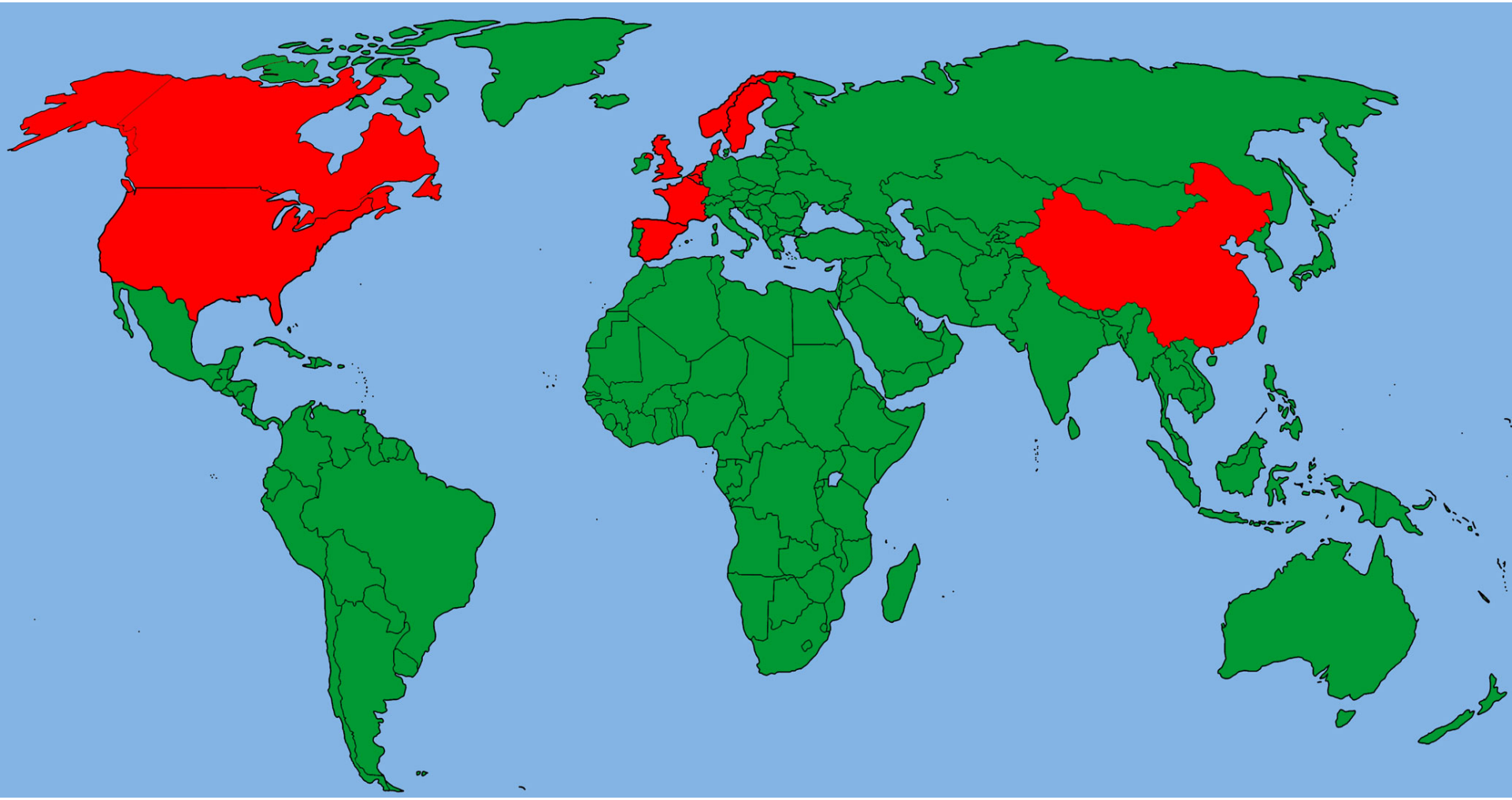
Amino Asit Değişikliği	Dirençli İlaçlar
M220I, M220V, M220K, M220T	ITC'a dirençli ve POS'a, VOR'a, RAV'a duyarlık azalması
G54R, G54E, G54W, G54V	ITC ve POS
L98H	Çoğul azol direnci olması (ITC, POS, VOR, ravukonazol)
G138C	**ITC, VRC ve uzun sureli tedaviler**

Mellado (2004,2005, 2007), Verweij 2007, Snelders 2009

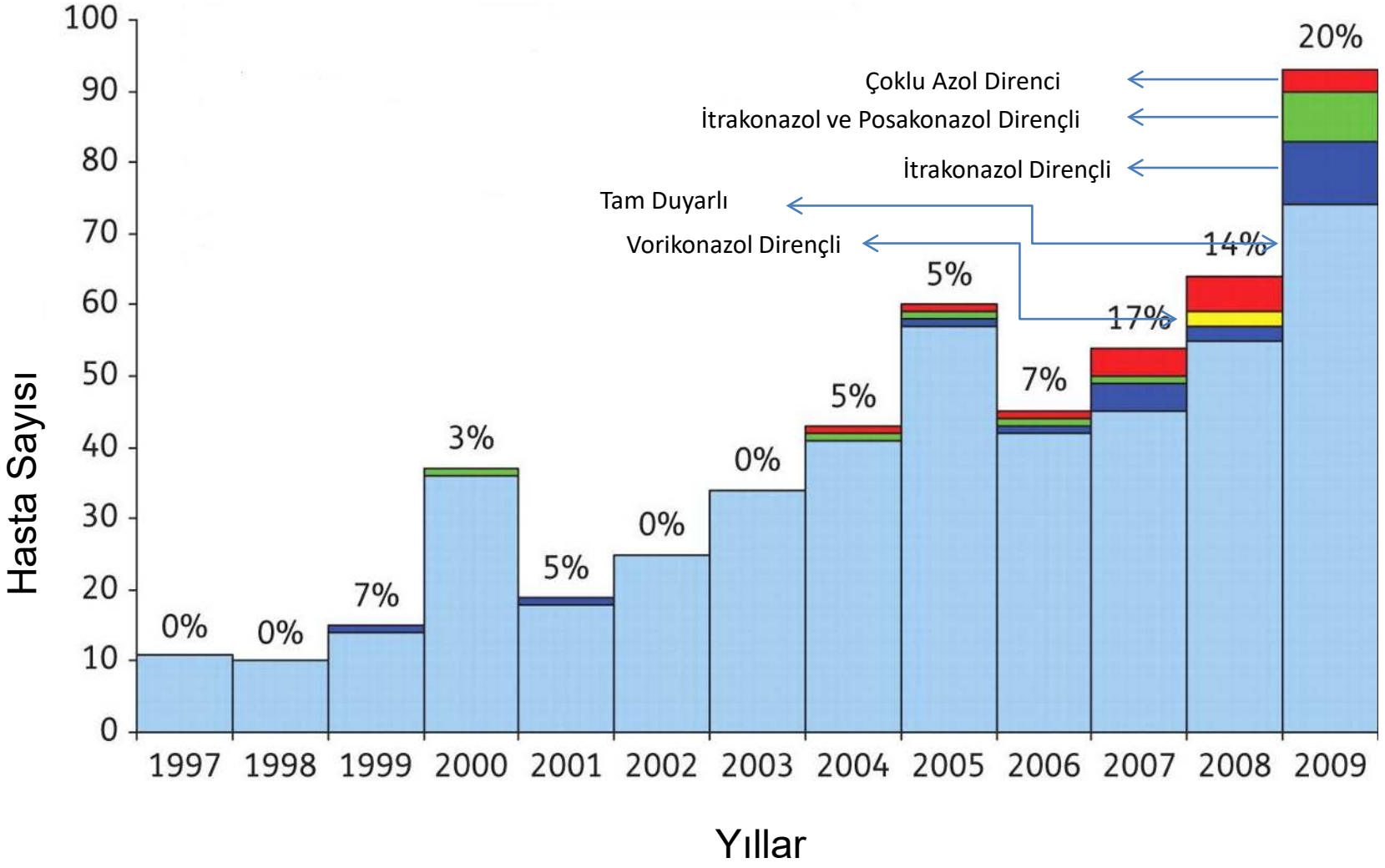
- Bazı merkezlerde görülme sıklığı giderek artmaktadır.
- In vivo ve in vitro
- Uzun süreli azol kullanımı ile ilişkilendirilmiştir.
- Moleküler mekanizması da çok iyi bilinmemektedir.



Klinikte Azol Dirençli *A.fumigatus* Sıklığı



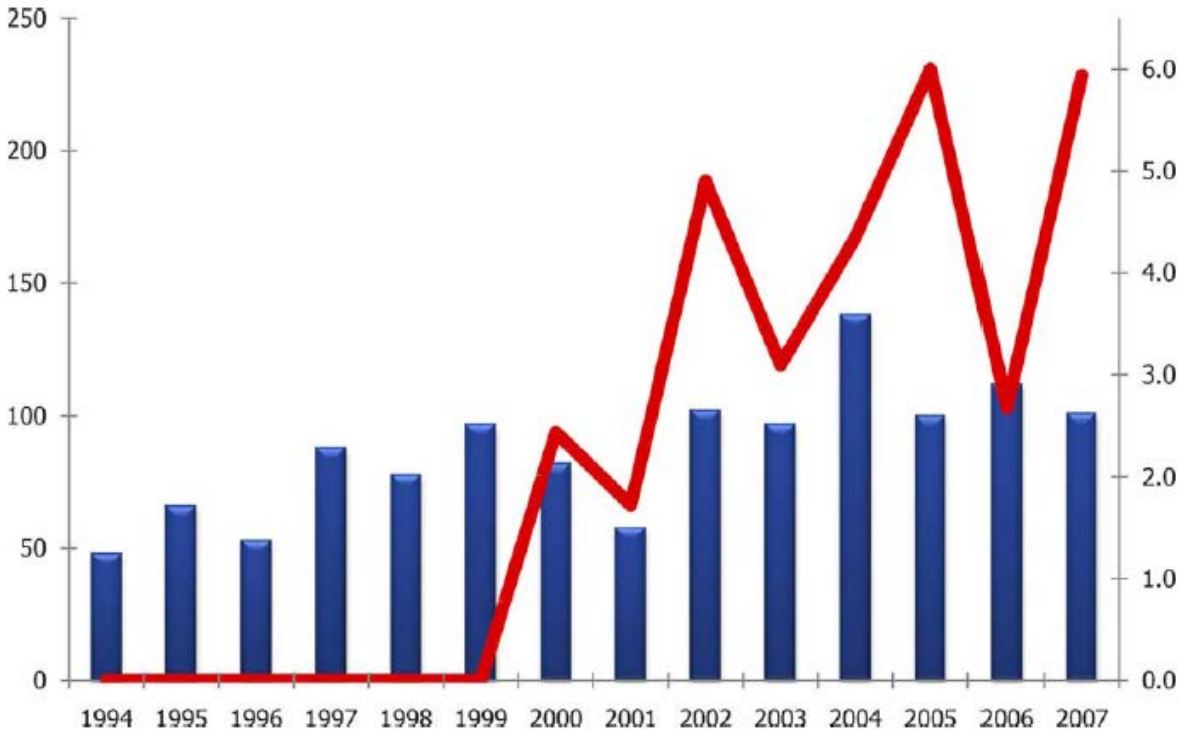
Aspergillus fumigatus (1997-2009)'da Azol Direnci Sıklığı



Bueid A et al. J. Antimicrob. Chemother. 2010;65:2116-2118

Aspergillus fumigatus'ta Azollere Karşı Gelişen Dirençin Sıklığı ve Direnç Mekanizmasının yaygınlığı

Direnç mekanizması: 32 İzolatın 30'unda (%94) TR/L98H Mutasyonu



Snelders E et al., PLoS Med 2008;5:e219

Azole resistance in *Aspergillus fumigatus*: a growing public health concern

Edith Vermeulen[a], *Katrien Lagrou*[a,b], *and Paul E. Verweij*[c]

Purpose of review
Reports from the end of the 2000s forced the medical community to take azole resistance in *Aspergillus fumigatus* into account. Not only patients with chronic aspergillus disease, who develop resistance during long-term azole treatment, but also azole-naive patients are at risk, owing to the presence of resistant strains in the environment. The purpose of this review is to overview the latest findings concerning the origin, evolution, and implications of azole resistance in *A. fumigatus*.

Recent findings
TR_{34}/L98H is the predominant resistance mechanism of environmental origin in *A. fumigatus*. Recent epidemiological data show that this mechanism is an expanding problem, with reports from China, Iran, and India. However, the TR_{34}/L98H strains from the Middle East are genotypically different from the European isolates; their emergence is, therefore, not due to simple geographical spread of the 'European' isolates. A new environmental resistance mechanism, TR_{46}/Y121F/T289A, was detected in the Netherlands, conferring voriconazole resistance. In patients chronically treated with triazoles, the spectrum of resistance has become more diverse, with the emergence of non-*CYP51A*-mediated mechanisms. Central registration of treatment and outcome data of patients with resistant aspergillus disease are needed.

Summary
Azole resistance in *A. fumigatus* is evolving to a global health problem.

Keywords
aspergillosis, *Aspergillus fumigatus*, CYP51A, drug resistance, fungal

Curr Opin Inf Dis 2013; 26:493-500

Table 1. Rate of resistant isolates among clinical *Aspergillus fumigatus* isolates and prevalence of resistance in colonized or infected patients

Country, ref.	Study period	Study isolates	Resistance rate	Resistance prevalence	TR_{34}/L98H rate	TR_{34}/L98H prevalence
UK, [6]	1997–2007	Clinical isolates, irrespective of relevance; referral center for chronic/allergic aspergillosis	34/519 (6.6%)	20/400 (5%)	2/519 (0.4%)	2/400 (0.5%)
UK, [8]	2008–2009	Clinical isolates sent for susceptibility testing; referral center for chronic/allergic aspergillosis	64/230 (27.8%)	28/157 (17.8%)	0/230 (0%)	0/157 (0%)
The Netherlands, [12]	1994–2007	Clinical isolates, irrespective of relevance	63/2061 (3.1%)	45/1320 (3.4%)	–	39/1320 (3.0%)
The Netherlands, [13]	2007–2009	Clinical isolates, irrespective of relevance	82/1792 (4.6%)	63/1192 (5.3%)	74/1792 (4.1%)	57/1192 (4.8%)
The Netherlands, [14▪]	2009–2011	Clinical isolates, irrespective of relevance	–	63/921 (6.8%)	–	47/921[a] (5.1%)
Spain, [15]	2010–2011	Clinical isolates, irrespective of relevance	1/156 (0.6%)	–	–	–
Spain, [16▪]	1999–2011	Clinical isolates from proven or probable invasive aspergillosis or aspergilloma	6/343 (1.8%)	6/148 (4.1%)	0/343 (0%)	0/150 (0%)
Denmark, [10]	2007–2009	Clinical isolates from cystic fibrosis patients, irrespective of relevance	–	6/133 (4.5%)	–	2/133 (1.5%)
France, [17]	2006–2009	Clinical isolates from patients with hematological malignancy, irrespective of relevance	1/118 (0.8%)	1/89 (1.1%)	0/118 (0%)	0/89 (0%)
France, [11]	2010–2011	Clinical isolates from cystic fibrosis patients, irrespective of relevance	–	6/131 (4.6%)	–	2/131 (1.5%)
France, [18▪▪]	2010–2011	Clinical isolates from cystic fibrosis patients, irrespective of relevance	9/85 (10.6%)	4/50 (8.0%)	5/85 (5.9%)	3/50 (6%)
Germany, [19▪]	2011–2012	Clinical isolates irrespective of relevance	3.2% (17/527)	–	6/527 (1.1%)	–
Japan, [20▪]	1994–2010	Clinical isolates, irrespective of relevance (obtained from Pneumology Dept.)	11.2% (22/196)	–	0/196 (0%)	–
India, [21▪]	2005–2010	Clinical isolates from patients suspected of bronchopulmonary aspergillosis	2/103 (1.9%)	2/85 (2.4%)	2/103 (1.9%)	2/85 (2.4%)
Iran, [22▪]	2003–2009	Clinical isolates obtained from patients with aspergillus diseases	3.2% (4/124)	–	3/124 (2.4%)	–
USA, [23]	2001–2006	Isolates recovered from transplant recipients with proven or probable invasive aspergillosis	1/181 (0.6%)	–	–	–

Curr Opin Inf Dis 2013; 26:493-500

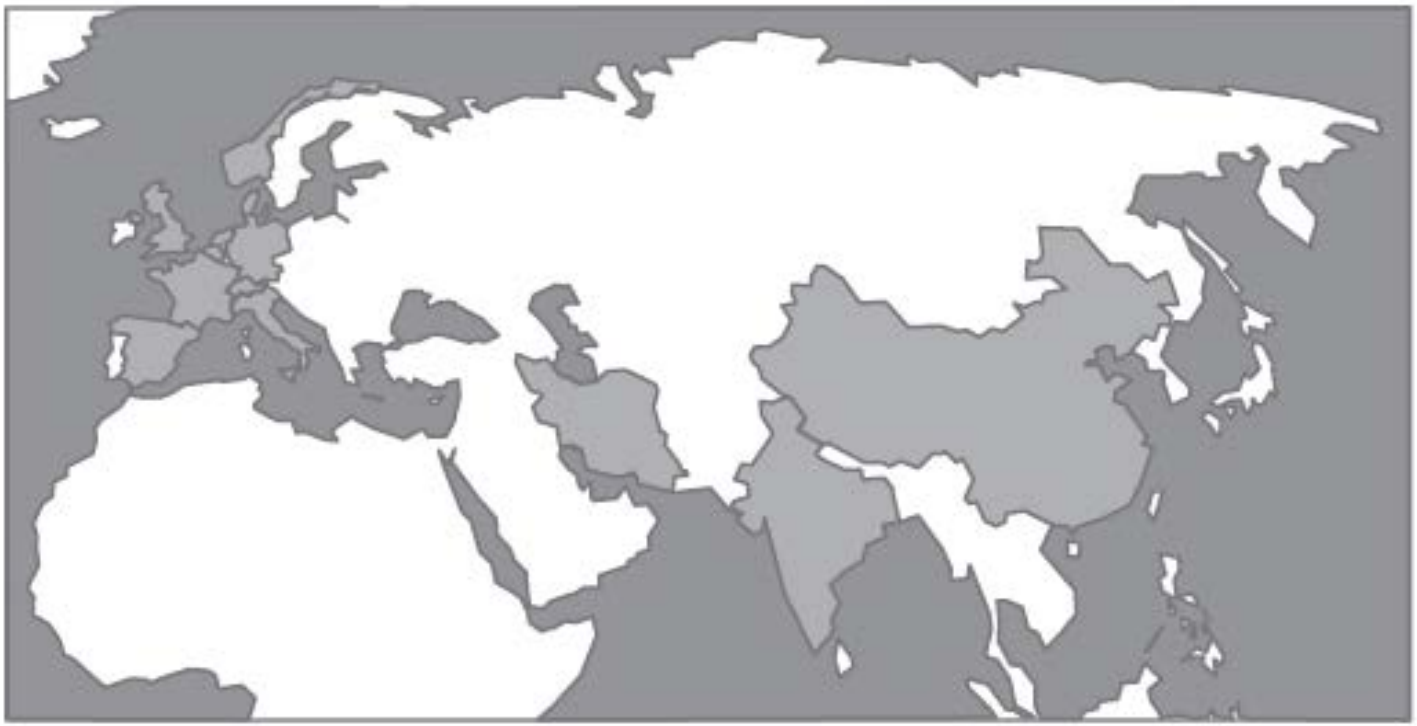


FIGURE 1. Geographical spread of the TR_{34}/L98H resistance mechanism (countries reporting TR_{34}/L98H marked in orange).

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Table 2. Evidence for a fungicide-driven route of resistance selection

	Reference
Agricultural triazole fungicides[a] have a comparable molecule structure to medical triazoles, binding to the same active site of the target enzyme	[35••]
Bioinformatic studies suggest that the presence of L98H not only hinders the docking of the medical triazoles but also of the triazole fungicides[a]	[35••]
TR_{34}/L98H also leads to resistance of agricultural triazole fungicides against *A. fumigatus*, in in-vitro susceptibility testing	[35••]
The authorization of five triazole fungicides[a] for use in the Netherlands (1990–1996) preceded the first TR_{34}/L98H isolate (in 1998)	[35••]
TR_{34}/L98H involves two genomic changes, which is unlikely to occur in a patient receiving azole therapy. The origin of tandem repeats is not well understood, but has also been found in phytopathogenic fungi, which lost susceptibility to azole fungicides.	[36•]
TR_{34}/L98H isolates have been reported from geographical areas that correspond with the highest usage of azole fungicides (Arendrup)	[37]

Curr Opin Inf Dis 2013; 26:493-500

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Original article

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

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ABSTRACT

Aspergillus fumigatus is the most important etiological agent of invasive aspergillosis. Recently, an increasing number of azole-resistant *A. fumigatus* isolates have been described in various countries. The prevalence of azole resistance was investigated in this study using our culture collection of *A. fumigatus* isolates collected between 1999 and 2012 from clinical specimens. Seven hundred and forty-six *A. fumigatus* isolates, collected from 419 patients, were investigated. First, all isolates were screened for resistance to itraconazole by subculturing on Sabouraud dextrose agar that contained 4 mg/L itraconazole. For isolates that grew on the itraconazole containing agar, the in vitro activities of amphotericin B, itraconazole, voriconazole and posaconazole were determined using the Clinical and Laboratory Standards Institute (CLSI) M38-A reference method. After PCR amplification, the full sequence of the *cyp51A* gene and its promoter region was determined for all in vitro azole-resistant isolates. Itraconazole resistance was found in 10.2% of the *A. fumigatus* isolates. From 2000 onwards, patients were observed annually with an itraconazole-resistant isolate. According to in vitro susceptibility tests, amphotericin B exhibited good activity against all isolates whereas the azoles were resistant. Sequence analysis of the promoter region and *CYP51A* gene indicated the presence of TR34/L98H in 86.8% (n = 66) of isolates. This initial analysis of the resistance mechanism of *A. fumigatus* from Turkey revealed a common TR34/L98H mutation in the *cyp51A* gene.

√

In conclusion, this study reveals that there are azole-resistant *A. fumigatus* strains in our clinical isolates and that the major resistance mechanism in these strains is the TR34/L98H mutation related with agricultural fungicides. Thus, we emphasize the need of further studies that show genetic relationship between clinical and environmental strains exactly. This study is the first study demonstrating TR34/L98H mutation in Turkey and, although it did not show a tendency towards increasing, it has been observed in nearly every year from 2000. It has to be kept in mind that resistant strains with TR34/L98H mutation can always be observed in invasive infections and azole compounds should be used carefully for prophylactic and treatment purposes. Clinics and laboratories should cooperate effectively to isolate the *A. fumigatus* and, in order to identify resistance, in vitro susceptibility tests should be performed when necessary.

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√

Discussion

The epidemiology of *Candida* infections has changed in recent years. Whilst the number of patients suffering from such infections has increased, the *Candida* species involved have become more numerous as NAC species begin to emerge. The various *Candida* species vary in their susceptibility to the available antifungal agents. The intrinsic resistance to antifungal therapy observed in some species, along with the development of acquired resistance during treatment in others, is becoming a major problem in the management of *Candida* infections. Antifungal susceptibility testing has therefore become essential for effective patient management and resistance surveillance.

Mycoses, 2015, 58 (Suppl. 2), 2–13

Ekinokandin

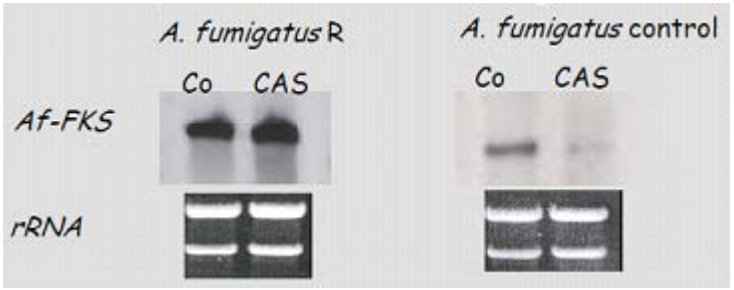
Ekinokandin Direnci

Glukan sentazı kodlayan FKS1 genindeki mutasyonlar

-S678Y laboratuvar kaynaklı mutant

-S678Plaboratuvar kaynaklı mutant

Genin aşırı kodlanması/ekspresyonu



Co: Tedavisiz A.fumigatus
CAS: KASP ile tedavi edilmiş A.fumigatus

Med Mycol 2005 AAC 2007

Kandida’da Ekinokandin Direnci

Fks1/2’nin **HS1 ve HS2 bölgeleri kandidalarda direnç** ile ilişkili bulunmuştur.

Candida albicans gibi diploid organizmaların hem homozigot hem heterozigot mutasyonları dirence neden olur.

Belirgin mutasyonlar tüm ekinokandinlar arasında çapraz dirence neden olur.

Drug Resist Updates 2007;10:121-30.

FKS1 Mutasyonu İlaç Duyarlığının Azalmasını Yansıtır ve *C.albicans*'da GS Enzim Kinetiği Etkiler

Özellik	**Antifungal İlaç**	**SC5314 (Parenteral)**	**A15-10 (S645P)**
MİK (µg/mL)	**ANF** **KASPO** **MİKA**	**0.08** **0.42** **0.05**	**4.0** **8.0** **4.0**
Ki (ng/mL)		**1.33** **2.97** **27.97**	**2563.7** **1358.0** **2249.5**
Vmaks (nmol/min)		**6.717**	**3.263**
Km (mM)		**0.125**	**0.091**

AAC2009;53:112-22.

Edinilmiş Antifungal Direnç

	Azoller	**Ekinokandinler**	**Amfoterisin B**
Hedef	P450 demetilaz	Glukan sentaz	Ergosterol
Hedef Gen Mutasyonu	CYP51A	FKS1	
Hedef üst REGÜLASYON	CYP51A+ Promotor	√	
Effluks Pompası	√		

Kandida ve Aspergillus İzolatlarında Direnç Mekanizmasını Tetikleyen Genler

	Genetic target		
	Candida		Aspergillus
Triazoles			
• **Target site mutations**	C. albicans	Erg11	Cyp51A
• **Target site upregulation**	C. albicans	Erg11	Cyp51A
• **Drug efflux transporters**			
ABC	C. albicans	Cdr1,Cdr2	Mdr1, Mdr4
	C. glabrata	Cdr1, Cdr2, Snq2	
MFS	C. albicans	Mdr1	Mdr3
• **Transcription factors**			
ABC	C. albicans	Tac1	
	C. glabrata	Pdr1	
MFS	C. albicans	Mrr1	
ERG	C. albicans	UpC2	
Chromosomal aneuploidy	C. albicans	**Chromosome 5**	
Echinocandins			
Target site mutations	C. albicans	Fks1	Fks1
	C. glabrata	Fks1, Fks2	

Current Opinion in Infectious Diseases 2009,22:568–573

Aspergillus fumigatus İzolatlarında

Genotype / Drug	G54X	G54W	L98X	TR/L98X	G138X	G138C
Itraconazole	R	R	S	R	R	R
Voriconazole	S	S	S	R	R	R
Posaconazole	S	R	S	S	S	S
Ravuconazole	S	S	S	R	R	R

Current Opinion in Infectious Diseases 2009,22:568–573

Dinlediğiniz için teşekkür ederim.