

Rehberler Eşliğinde Antifungal Tedavi

Dr. Murat Akova

**Hacettepe Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları AD,
Ankara**





Courtesy of Ben de Pauw

Guidelines Practice vs Praxis



Courtesy of Ben de Pauw

A multidisciplinary team approach to the management of patients with suspected or diagnosed invasive fungal disease

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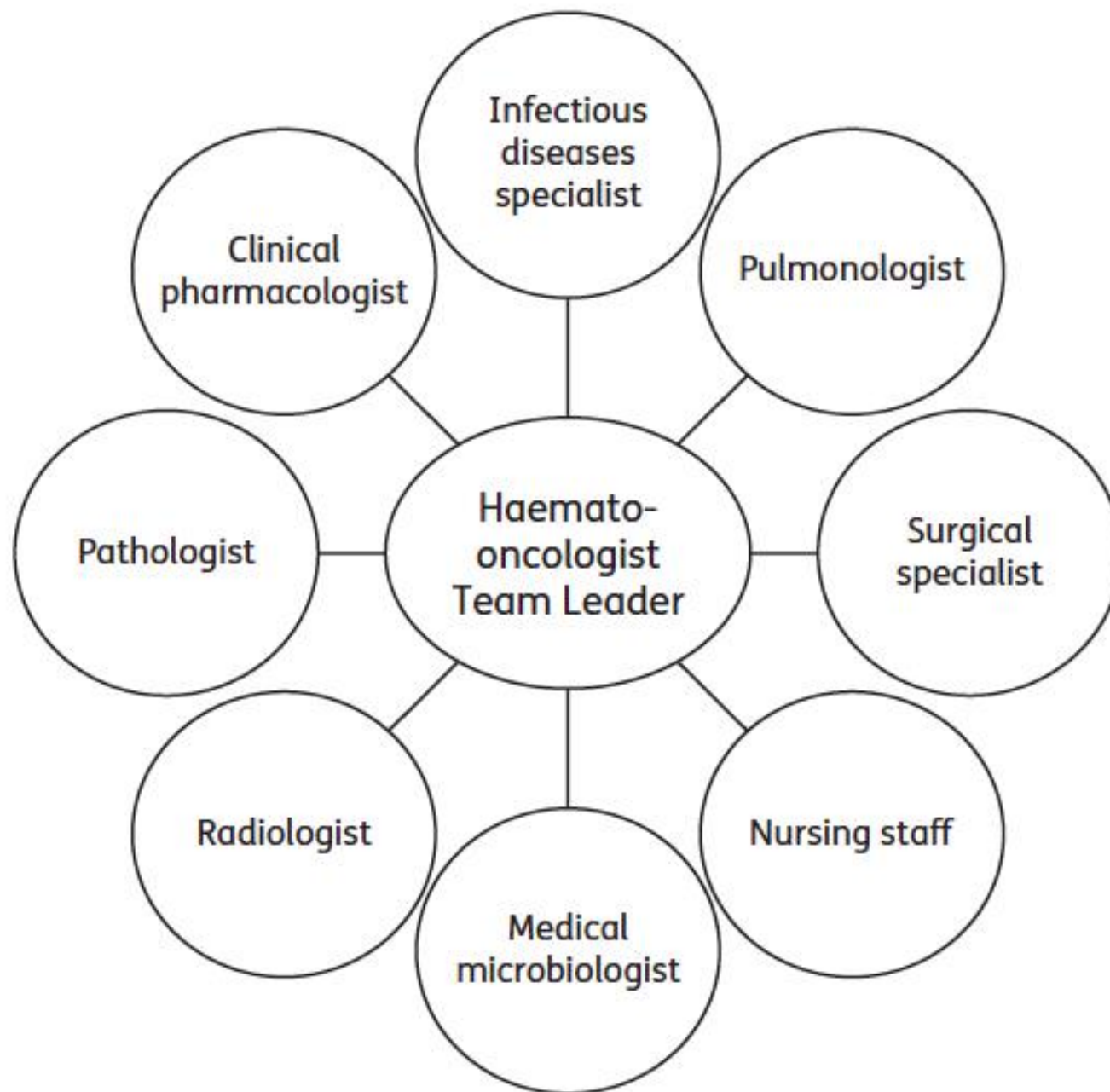
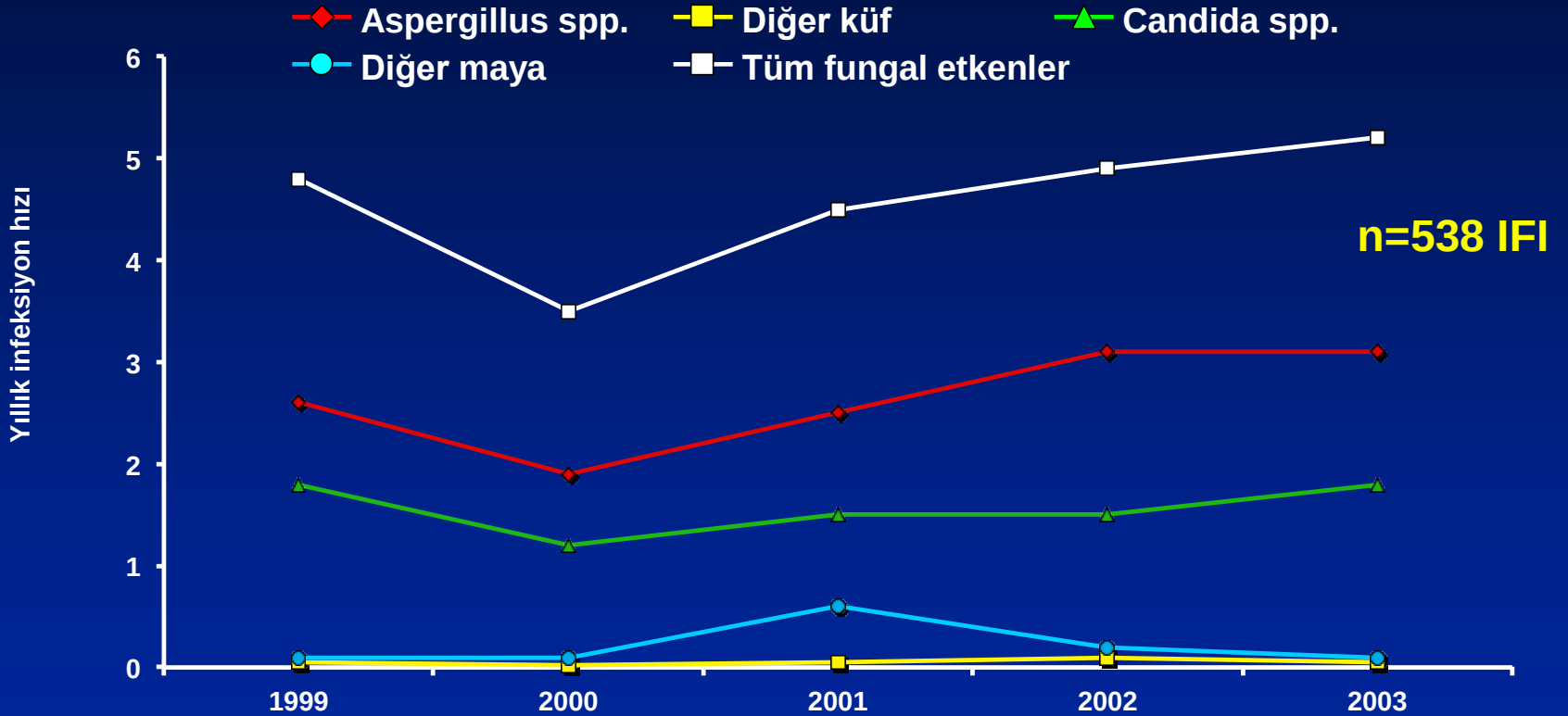


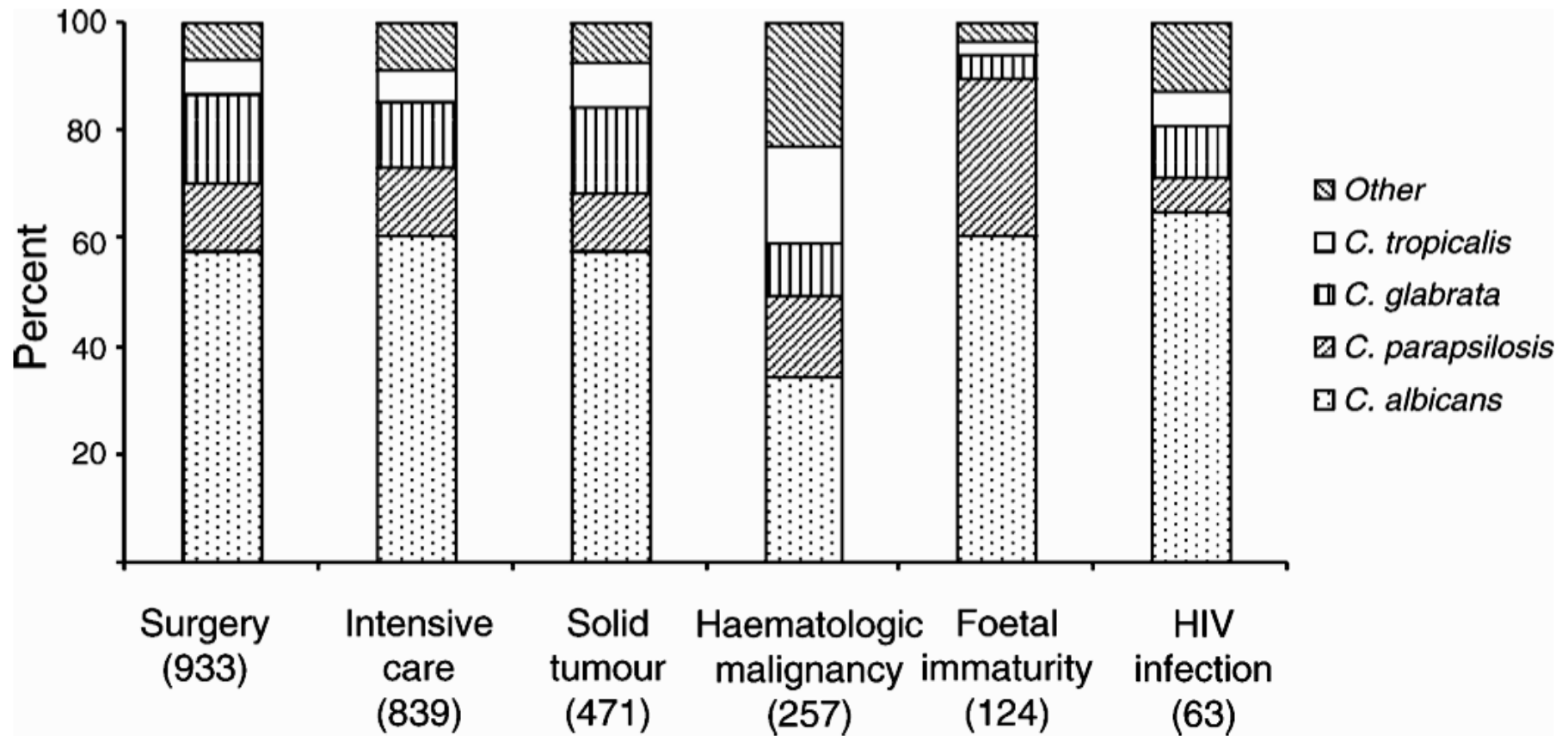
Figure 1. Diagram of the key members of the IFD-MDT.

Hematolojik Kanserli Hastalarda İnvaziv Fungal İnfeksiyon Sıklığı



Avrupa'da Kandidemi

Kandida Türlerinin Dağılımı

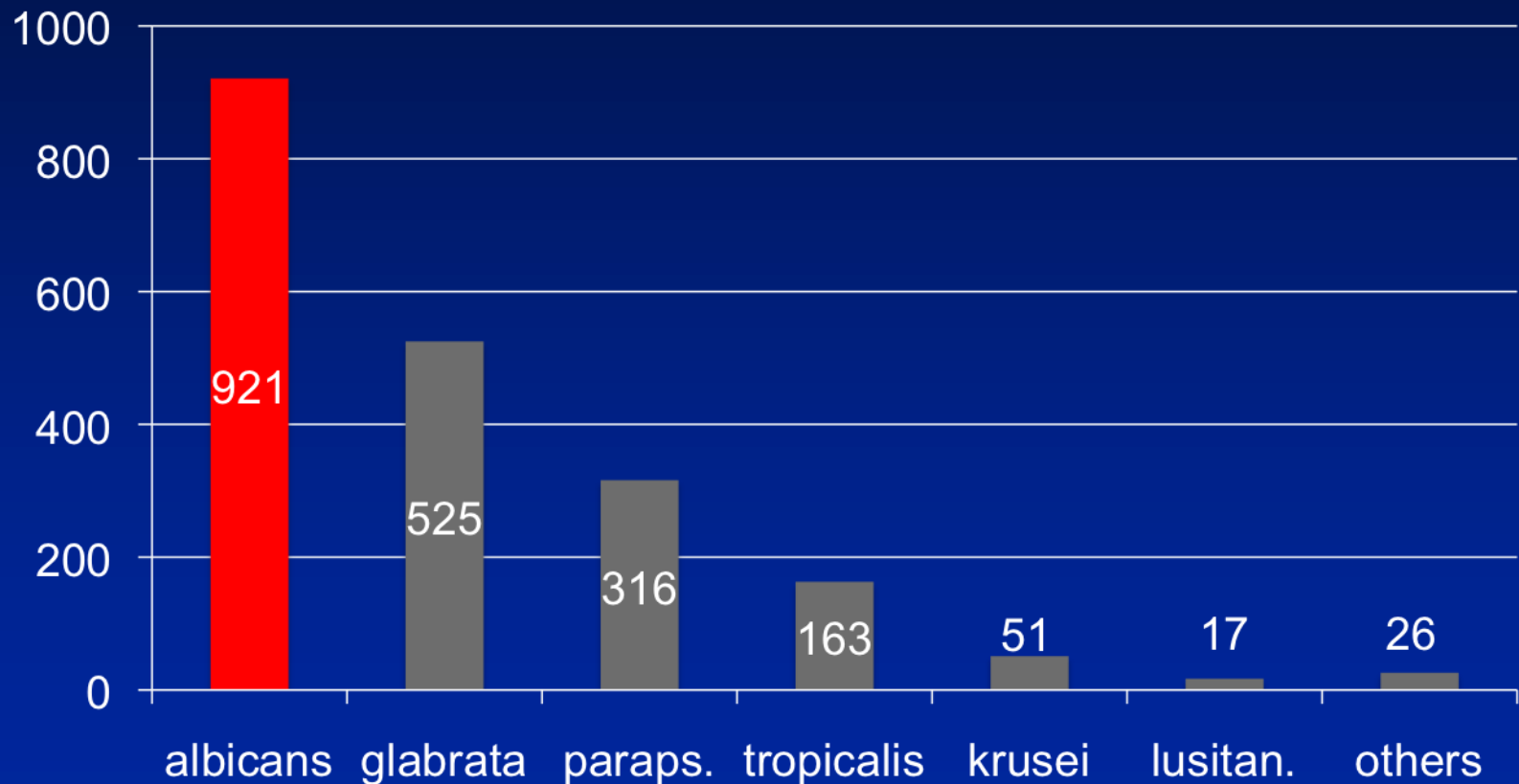


“Prospective Antifungal Therapy (PATH) Alliance” Çalışmasında Kandidemi

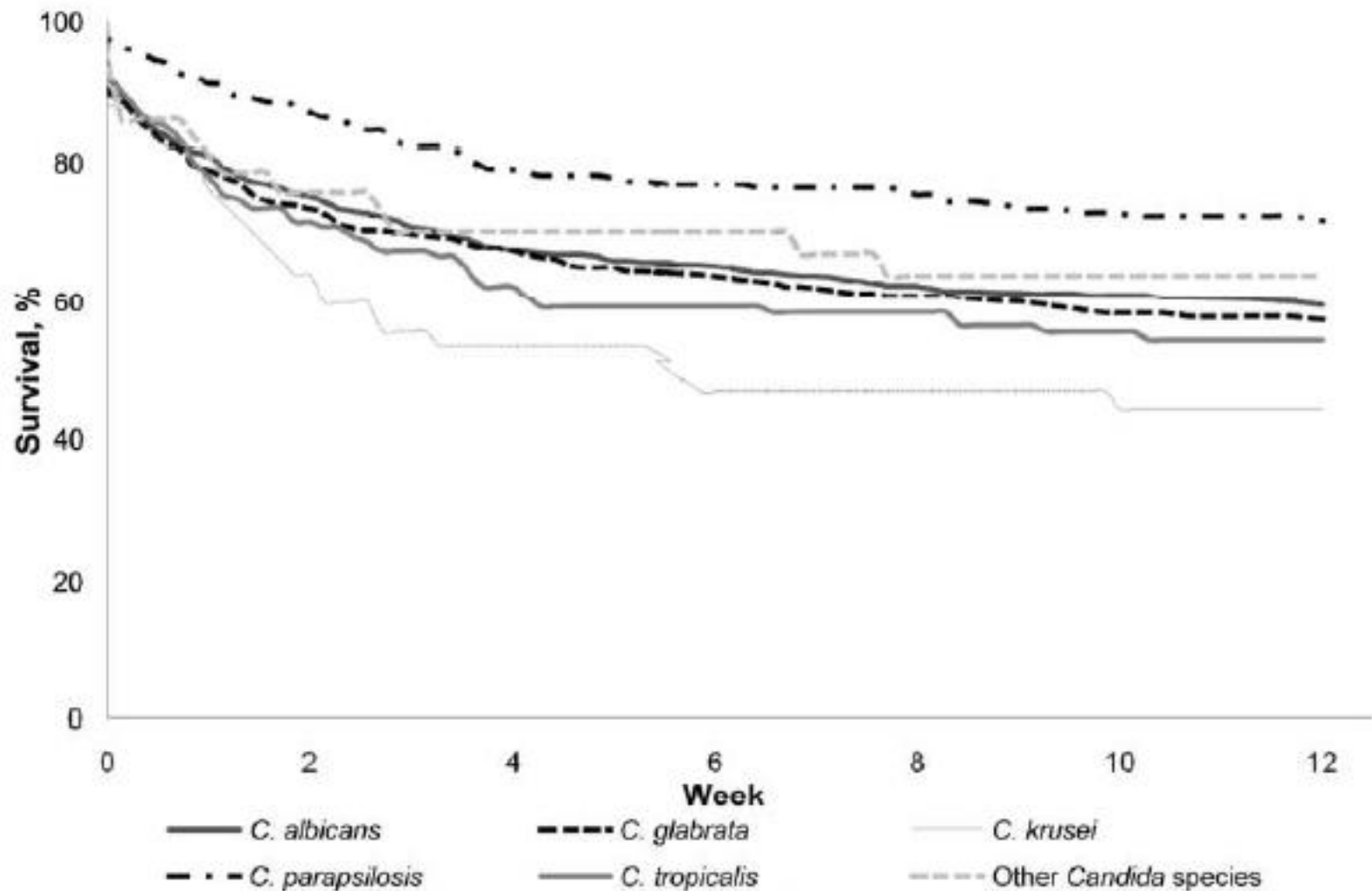
- 2019 hasta
 - 1 Temmuz 2004-5 Mart 2008
- *C. albicans* (%45.6)
- 12. haftada kaba mortalite %35.2
 - *C. parapsilosis* %23.7
 - *C. krusei* %52.9

Kandida Türlerinin Dağılımı

“PATH Registry”



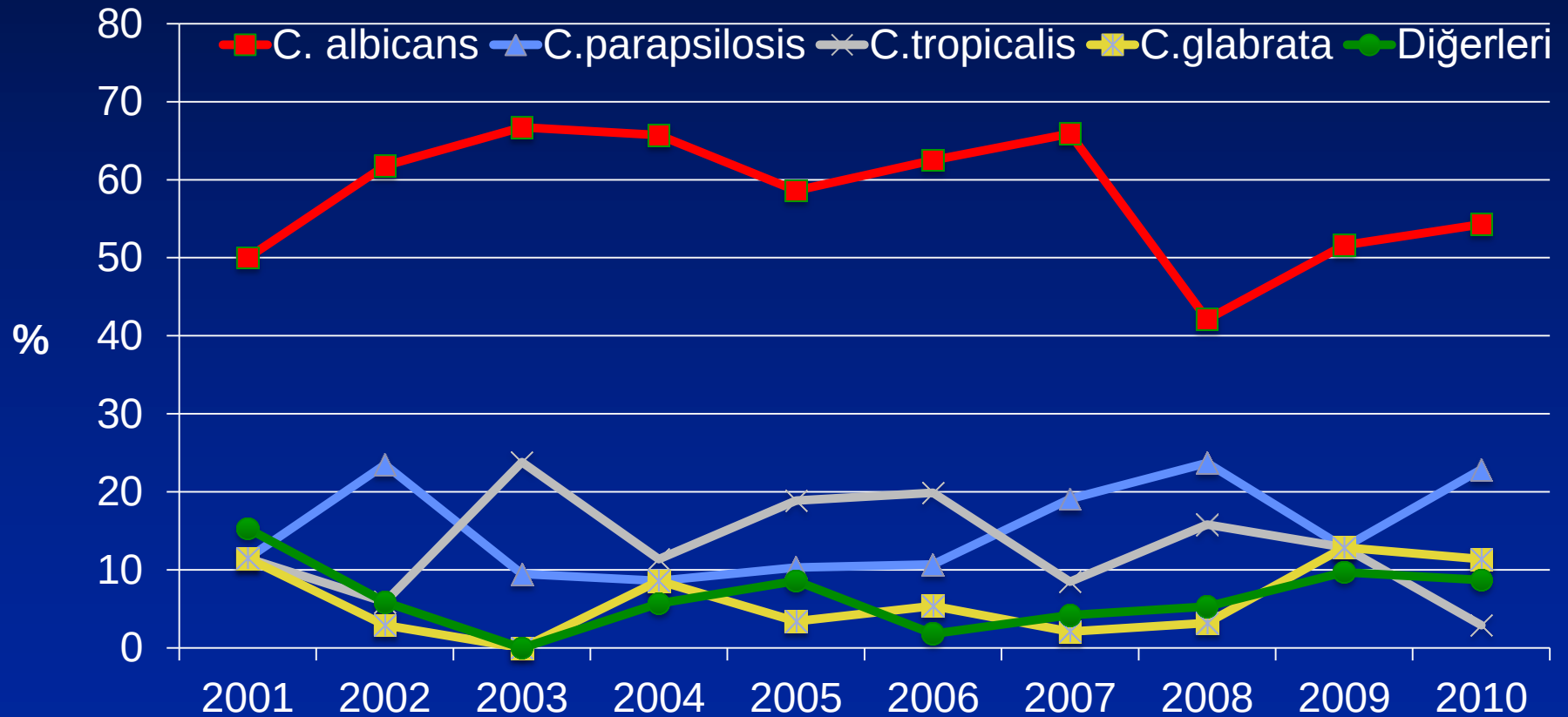
Kandidemili Hastalarda 12. Haftada Sağkalım-PATH



Hacettepe'de Kandidemi

- 2001-2011, retrospektif analiz
- 18.426 pozitif kan kültürü
 - 858 kandida-pozitif kan kültürü
 - 381 izolat, tek hasta, ilk atak
 - Kandida en sık üretilen 5. patojen

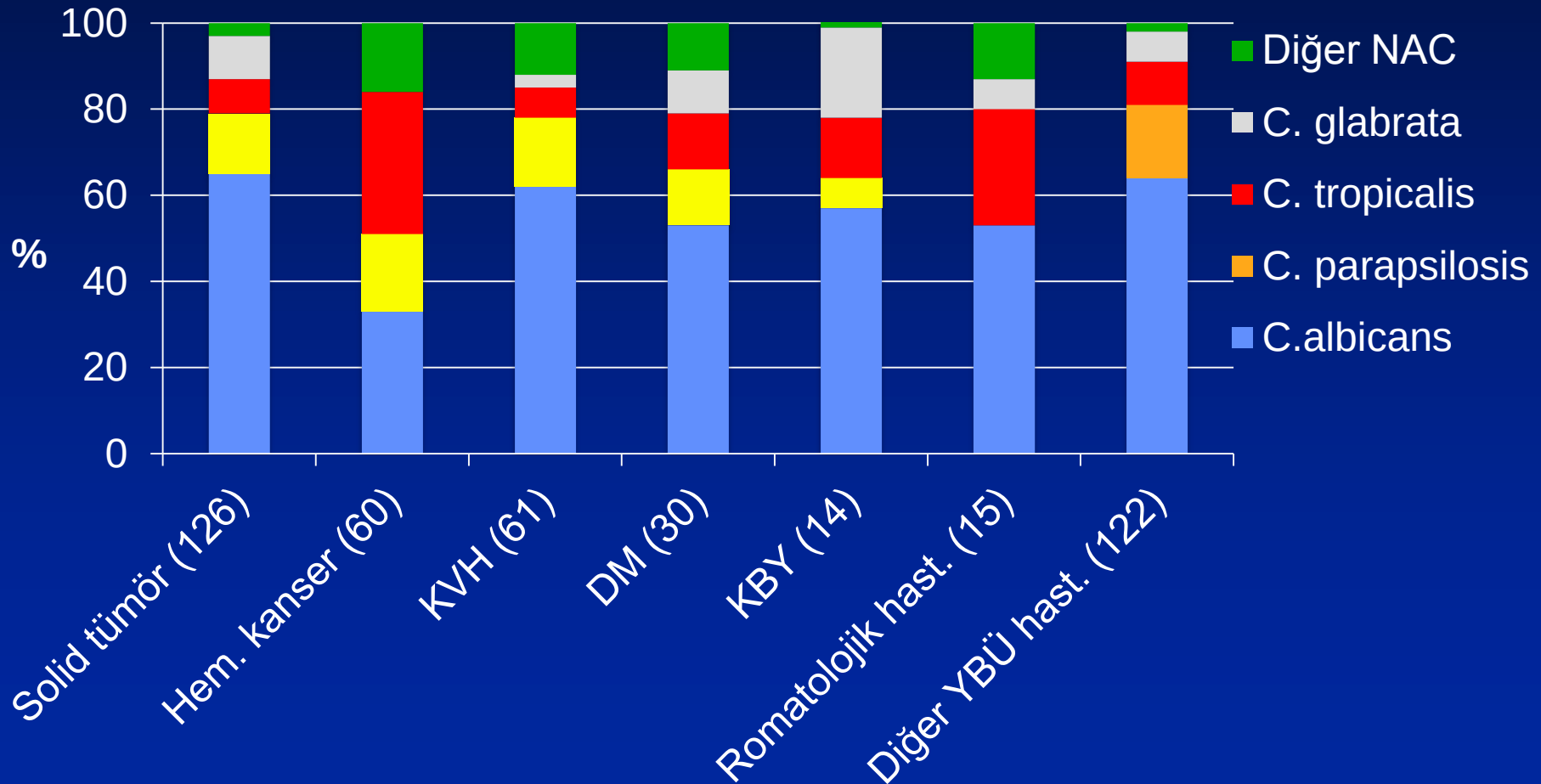
Hacettepe'de Kandidemi İzolatları n=381



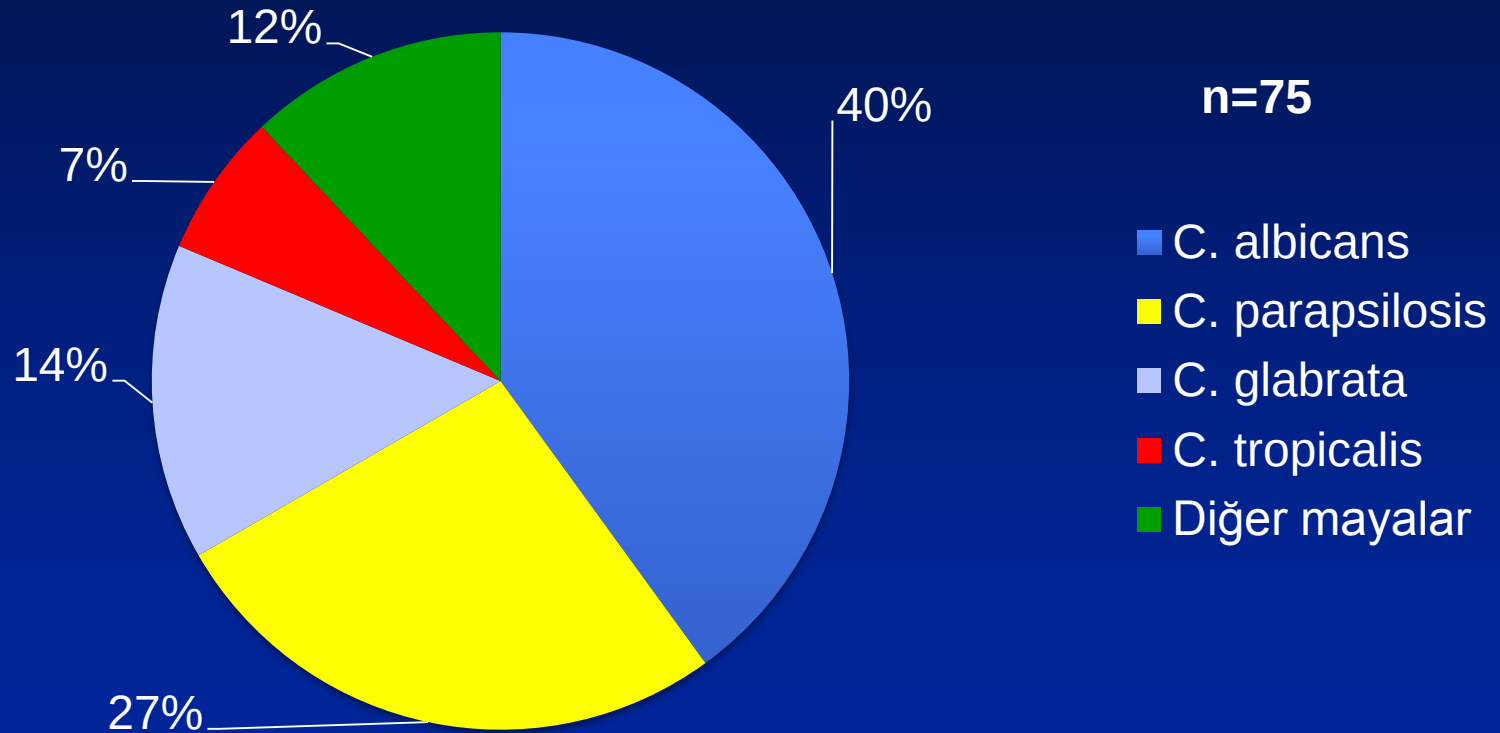
Alp S, Arıkan-Akdağlı S & Akova M. 2012

Kandida Türleri ve Altta Yatan Hastalıklar

Hacettepe 2001-2010



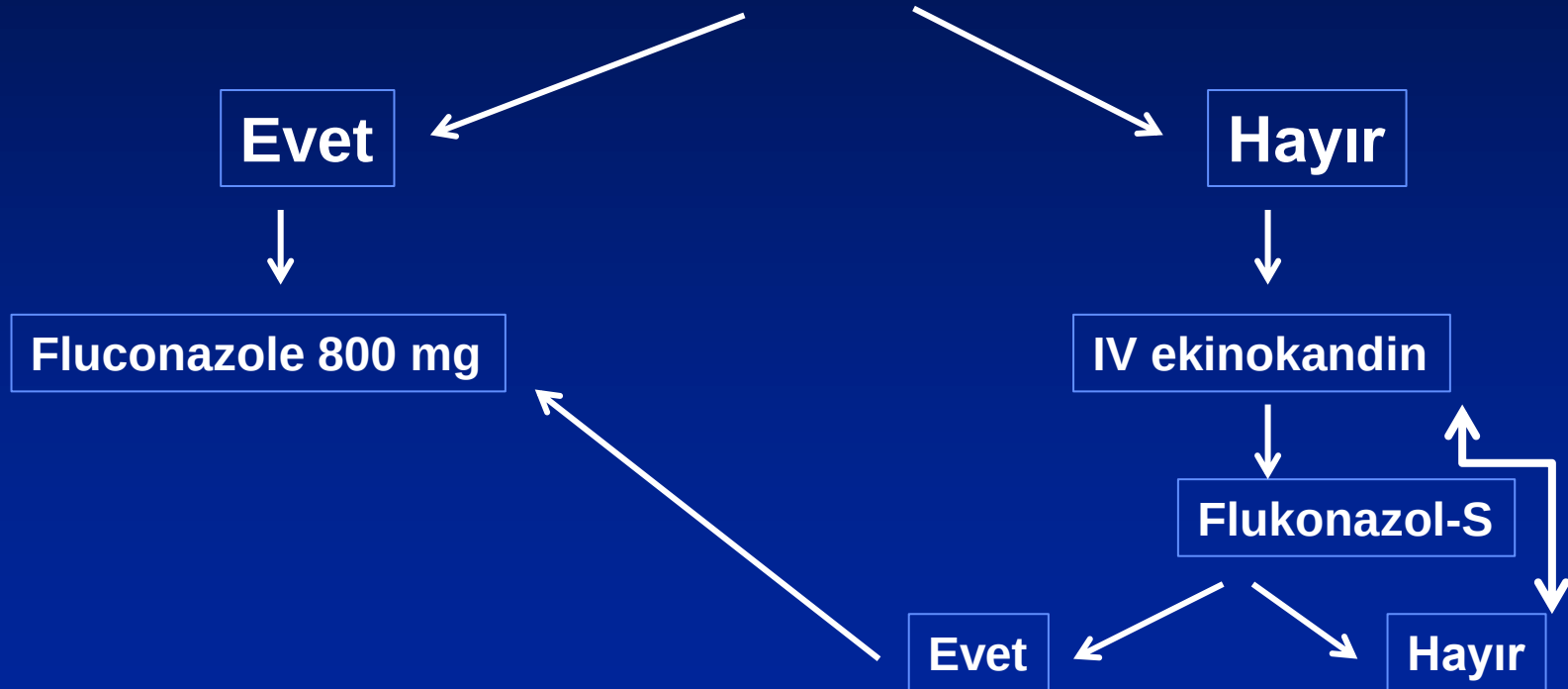
Kandidemi İzolatları Hacettepe 2013



İnvaziv Kandidiyazis Tedavisi

IDSA 2009

Flukonazol-S suş olası
Hasta stabil

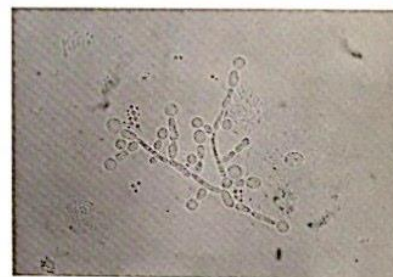


CMI CLINICAL MICROBIOLOGY AND INFECTION

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ESCMID Guideline for the Diagnosis and Management of *Candida* Diseases



ESCMID
THE OFFICIAL PUBLICATION OF THE
EUROPEAN SOCIETY OF CLINICAL
MICROBIOLOGY AND INFECTIOUS DISEASES

ESCMID Guideline for the Diagnosis & Management of Candida Diseases 2012

Authors: Murat Akova, Maiken Arendrup, Sevtap Arikan-Akdogli, Matteo Bassetti, Jacque Bille, Thierry Calandra, Elio Castagnola, Oliver A. Cornely, Manuel Cuenca-Estrella, Peter Donnelly, Jorge Garbino, Andreas Groll, Raoul Herbrecht, William Hope, Henrik Elvang Jensen, Bart-Jan Kullberg, Cornelia Lass-Flörl, Olivier Lortholary, Wouter Meersseman, Georgios Petrikos, Malcolm Richardson, Emmanuel Roilides, Andrew J. Ullmann, Paul Verweij, Claudio Viscoli

Main Coordinator: Andrew J. Ullmann



THE TEAM:

ESCMID Diagnostic & Management

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William Hope
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Olivier Lorth
France
Wouter Meer
Georgios Pet
Malcolm Rich
United Kingdom



Emmanuel Roilides, Aristotle University, Thessaloniki Greece

Paul Verweij, Radboud University, Nijmegen, Netherlands

Çalışma Grupları

Diagnostic procedure

Maiken Arendrup, Sevtap Arikan-Akdagli, Jacques Bille, **Manuel Cuenca-Estrella**, Peter Donnelly, Henrik Elvang Jensen, Cornelia Lass-Flörl, Malcolm Richardson, Paul Verweij

ICU (medical & surgical)

Other non-immunocompromised (medical & surgical), other immunocompromised situations

Matteo Bassetti, Thierry Calandra, **Oliver Cornely**, Jorge Garbino, Bart-Jan Kullberg, Wouter Meersseman

Paediatrics

PICU

Elio Castagnola, Andreas Groll, **William Hope**, Emmanuel Roilides

Haematology/Oncology

Murat Akova, Raoul Herbrecht, **Andrew Ullmann**, Claudio Viscoli

HIV/AIDS

Olivier Lortholary, Georgios Petrikos

TABLE 2. Strength of the ESCMID recommendation and quality of evidence

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized controlled trial
Level II*	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

*Added index:

_r: meta-analysis (or systematic review of randomized controlled trials).

_t: transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.

_h: comparator group: historical control.

_u: uncontrolled trials.

_a: published abstract (presented at an international symposium or meeting).

Allojeneik KHN Kandida Profilaksisi

	Intention: Morbidity reduction		Intention: Survival improvement	
	SoR	QoE	SoR	QoE
Intervention (anti-Candidal prophylaxis) during the neutropenic phase				
Fluconazole 400 mg qd if no prophylaxis is considered	A	I	A	I
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I
Posaconazole* 200 mg tid	A	II _t	B	II _t
Voriconazole* 200 mg bid	A	I	C	I
Caspofungin* 70/50 mg qd	C	II _u	C	III
Micafungin* 50 mg qd	A	I	C	I
Anidulafungin	NR	ND	NR	ND
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	B	II	C	III
Intervention (anti-Candidal prophylaxis) during the first 100 days without GVHD and neutrophil recovery				
Fluconazole 400 mg qd	A	I	A	I
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I
Posaconazole* 200 mg tid	C	III	C	III
Voriconazole* 200 mg bid	A	I	C	I
Caspofungin* 70/50 mg qd	C	II _u	C	II _u
Micafungin* 50 mg	C	III	C	III
Anidulafungin	NR	ND	NR	ND
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	C	III	C	III
Intervention (anti-Candidal prophylaxis) in GVHD				
Fluconazole 400 mg qd	A	I	C	I
Itraconazole* 2.5 mg/kg oral solution tid	C	I	C	I
Posaconazole* 200 mg tid	A	I	B	I
Voriconazole* 200 mg bid	B	I	C	I
others	NR	ND	NR	ND

Ullmann AJ, Akova M, Herbrecht R, et al.
Clin Microbiol Infect 2012;18 (suppl.7):53-67

Otolog KHN ve Kemoterapiye Bağlı Nötropenik Hastada Kandida Profilaksisi

Intention	Situation	Autologous HCT		Severe and prolonged neutropenia	
		Intervention	SoR/QoE	Intervention	SoR/QoE
Morbidity reduction or survival advantage*	Neutropenia*	Any prophylaxis	DIII	Any prophylaxis	DIII
		Any prophylaxis	DIII	Any prophylaxis	DIII
		Fluconazole	ND	Fluconazole	CI
		Itraconazole	CII	Itraconazole	CI
		Posaconazole	CIII	Posaconazole	CIII
		Voriconazole	ND	Voriconazole	ND
		Anidulafungin	ND	Anidulafungin	ND
		Caspofungin	ND	Caspofungin	CI
		Micafungin	ND	Micafungin	ND
		Nystatin	DIII	Nystatin	DII
		Any amphotericin B formulation	ND	Any amphotericin B formulation	DI

*If an institution wishes prophylaxis, weak recommendations for selected antifungal agents are provided.

ND, no data.

Olası Kandidemi İçin Empirik Tedavi

Intention	Intervention	Allogeneic HCT included	SoR	QoE
Morbidity reduction	Liposomal amphotericin B (3 mg/kg/day)	Yes	A	I
	Caspofungin (70 mg on day 1 then 50 mg)	Yes	A	I
	Amphotericin B colloidal dispersion (4 mg/kg/day)	Yes	C	I
	Amphotericin B lipid complex (5 mg/kg/day)	Yes	B	I
	Itraconazole (200 mg iv q12h on day 1 & 2 then 200 mg iv/day)	ND	B	I
	Voriconazole (2 × 6 mg/kg on day 1 then 2 × 3 mg/kg/day) [§]	Yes	B	I
	Fluconazole (400 mg/day)	ND	C*	I*
	Amphotericin B deoxycholate (0.5–1.0 mg/kg/day)	Yes	D	II _t
	Micafungin (100 mg)	Yes	B	II
	Anidulafungin	ND	NR	

*Limited use since fluconazole has no mould activity. Application requires appropriate work-up to rule out mould disease.
NR, no recommendation; ND, no data available, [§], dosis according to trial [48].

İnvaziv Kandidiyazis'te Hedeflenmiş Tedavi

Intention	Intervention	SoR	QoE	Comment
Morbidity reduction and survival improvement	Fluconazole	C	II _t	Caution regarding resistance. Fluconazole should rather be considered as a step-down treatment option
	Itraconazole	D	III	Only abstract in non-neutropenics
	Posaconazole	D	III	One case report in a non-neutropenic
	Voriconazole	C	II _t	Alternative agent due to better susceptibility data in comparison with fluconazole but limited clinical data
	Amphotericin B colloid dispersion	C	III	Considerable nephrotoxicity
	Amphotericin B deoxycholate	D	II _t	Unacceptable toxicity
	Amphotericin B lipid complex	C	II _a	Considerable nephrotoxicity
	Anidulafungin	B	II _t	<3% of the participants were neutropenic
	Caspofungin	A	II _t	~10% of the participants were neutropenic
	Liposomal amphotericin B	B	II _t	
	Micafungin	A	II _t	~10% of the participants were neutropenic consider EMA warning

Kronik Dissemine Kandidiyazis Tedavisi

Intention	Intervention	Duration	SoR/QoE	Comments
Eradication	Fluconazole	Reported duration minimum 3 months	BIII	[125,126]
	Other azoles (if susceptibility is expected)		BIII	Lacking data
	Amphotericin B deoxycholate		DIII	Toxicity issues
	Lipid formulations of amphotericin B	8 weeks	AIII	Better exposure
Defervesce	Steroid therapy	Until defervesce	CIII	

Ullmann AJ, Akova M, Herbrecht R, et al. Clin Microbiol Infect 2012;18 (suppl.7):53-67

Kateterle İlişkili Kandidemi Tedavisi

Intention	Intervention	SoR/QoE	Comment
Survival advantage	Early catheter removal	All _u	Retention and high APACHE II and thrombocytopenia also associated with higher mortality.
Morbidity reduction	Catheter retention	CII _t	Patients in trials treated with echinocandins and CVC retention had equal outcome (low numbers)
	If catheter retention use echinocandins or liposomal amphotericin B, not azoles or amphotericin B deoxycholate	CII _t	Worse outcome in non echinocandins trials
	Other implanted hardware (pace-maker, port-a-cath)	CIII	Keep unless proven associated with candidaemia. No published data available

Ullmann AJ, Akova M, Herbrecht R, et al. Clin Microbiol Infect 2012;18 (suppl.7):53-67

Kandidemide Tedavi Süresi

- Son pozitif kan kültüründen sonra en az 14 gün ve hastalığa ilişkin belirti ve bulguların kaybolması koşuluyla
 - Nötropenik olmayan hastalarda **BII**
 - Nötropenik hastalarda **CIII**



Introduction to ECIL

from ECIL1 to ECIL 4



4th European Conference on Infections in Leukemia

ECIL 1: Juan-les-Pins, France, Sept 30-Oct 1st, 2005

59 experts from 24 European countries, one from Australia

ECIL 2: Juan-les-Pins, Sept 28-29th, 2007

53 experts from 24 European countries, one from Australia

ECIL 3: Juan-les-Pins, France, Sept 25-26th, 2009

57 experts from 18 European countries, 2 from Russia

ECIL 4: Sept 9-10th, 2011

53 experts from 18 European countries, one from Russia



ECIL-5

19-21 September 2013,
Juan-les-Pins



5th European Conference on
Infections in Leukaemia

CDC Grading system used from ECIL3

Quality of evidence	Strength of recommendations
I Evidence from ≥ 1 properly randomized, controlled trial II Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series studies; or from dramatic results from uncontrolled experiments III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	A Good evidence to support a recommendation for or against use B Moderate evidence support a recommendation for or against use C Poor evidence to support a recommendation



Candidemia in hematologic patients before species identification (ECIL-1 to 3)

	Overall population	Hematological pts
Micafungin	A I	B II A II
Anidulafungin	A I	B II A III
Caspofungin	A I	B II A II
AmBisome	A I	B II
ABLC, ABCD	A II	B II
AmB deoxycholate	A I * C I	C III * C II
Fluconazole	A I **	C III
Voriconazole	A I ***	B II

* D III if concomitant nephrotoxic drug and E III if renal impairment

** Not in severely ill patients or in patients with previous azole prophylaxis

*** Not in patients with previous azole prophylaxis



Candidemia after species identification (ECIL-1 to 3) (1/2)

Overall population Hematological
pts

Micafungin /
Caspofungin

C albicans

~~A I~~ A I

~~B II~~ A II

C glabrata

~~B I~~ A II

~~B II~~ A III

C krusei

B I

~~B II~~ A II

C. parapsilosis

B II

B III

Anidulafungin

C albicans

~~A I~~ A I

~~B II~~ A III

C glabrata

~~B I~~ A II

~~B II~~ A III

C krusei

B I

~~B II~~ A III

C. parapsilosis

B II

B III



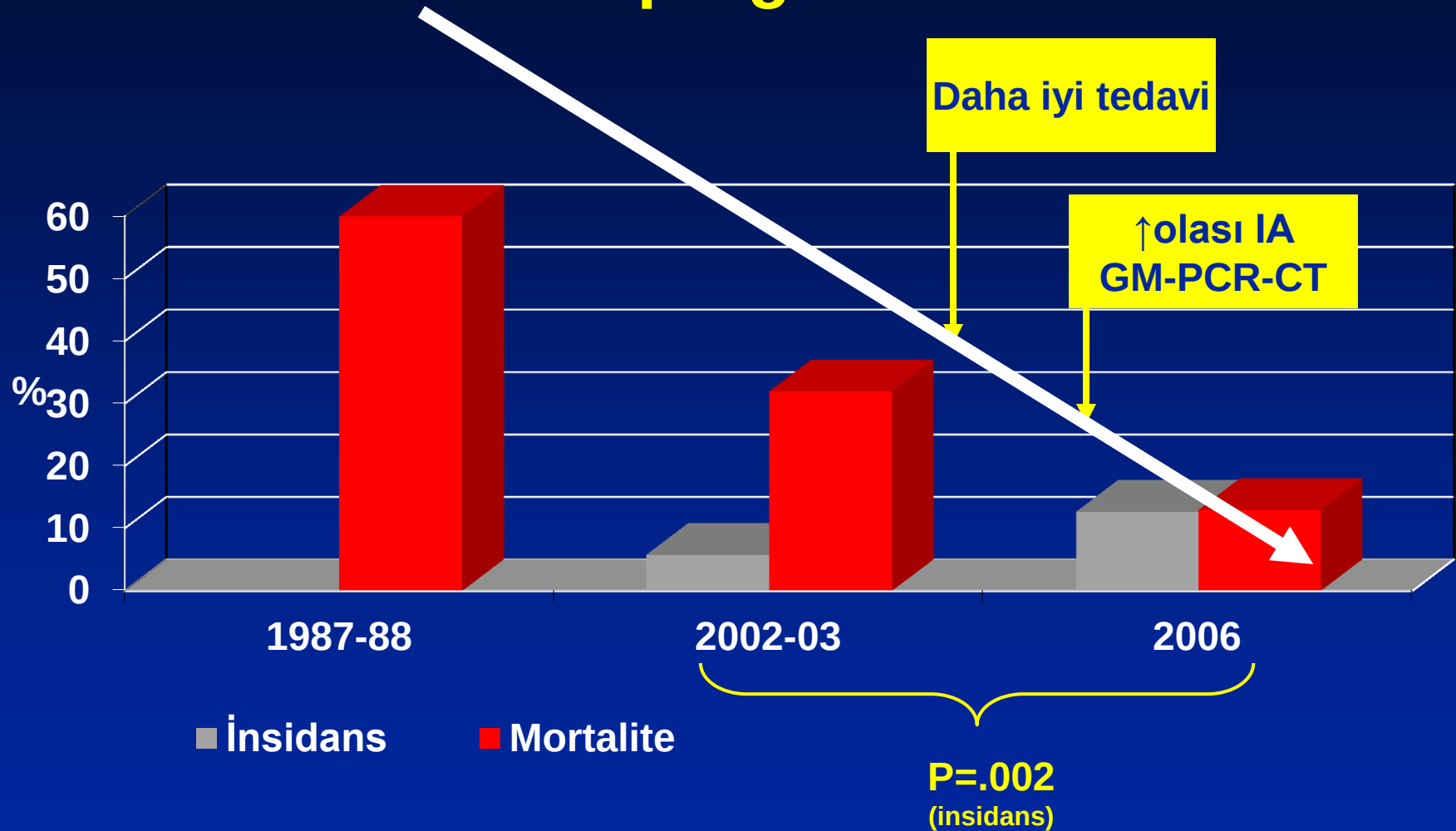
Candidemia after species identification (ECIL-3) (2/2)

		Overall population	Hematological pts
AmBisome	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
ABCD, ABLC	<i>C albicans</i>	A II	B II
	<i>C glabrata</i>	B II	B II
	<i>C krusei</i>	B II	B II
AmB deoxycholate	<i>C albicans</i>	A I* C I	C III* C II
	<i>C glabrata</i>	B I* C I	C III* C II
	<i>C krusei</i>	B I* C I	C III* C II
Fluconazole	<i>C albicans</i>	A I	C III
	<i>C glabrata</i>	C III	D III
	<i>C krusei</i>	E III	E III
	<i>C. parapsilosis</i>	A II	A III
Voriconazole	<i>C albicans</i>	A I	C III
	<i>C glabrata</i>	C III	C III
	<i>C krusei</i>	B I	C III

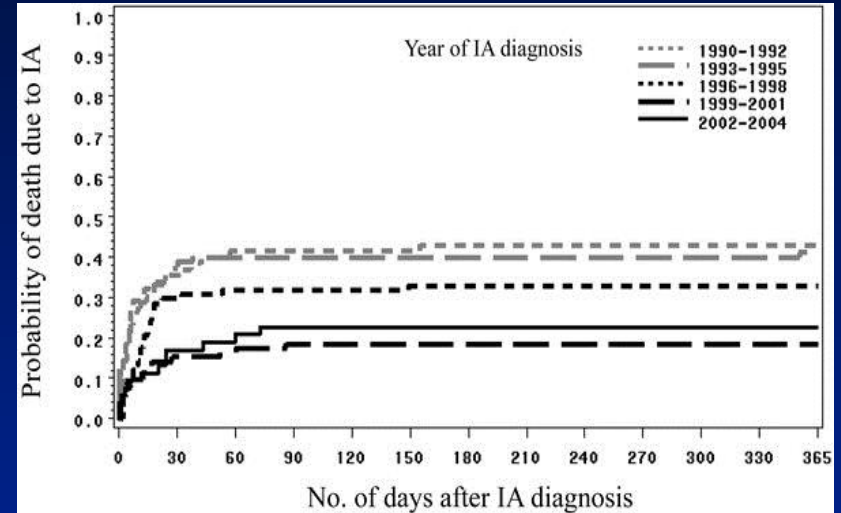
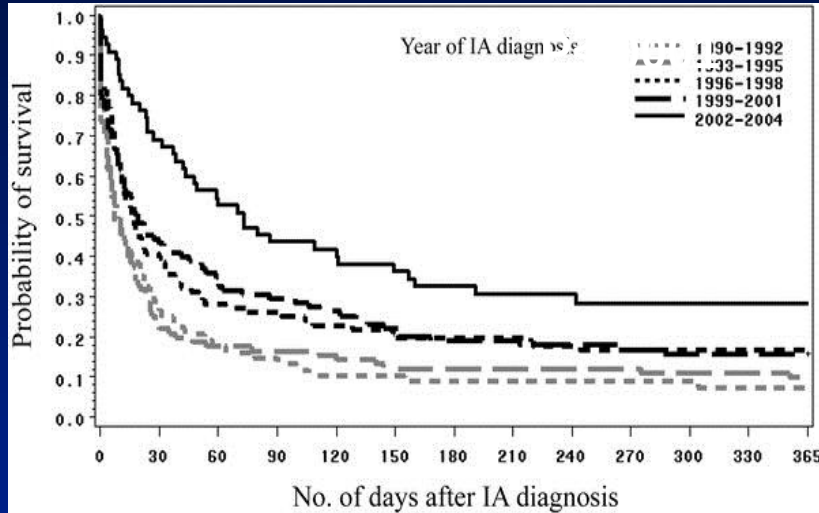
* DIII if concomitant nephrotoxic drug and EIII if renal impairment

İnvaziv Aspergillozis Tedavisinde Yenilikler

Akut Lösemili Hastalarda İnvaziv Aspergillozis



Kök Hücre Naklinde İnvaziv Aspergillozis'ten Sağkalım ve Prognostik Faktörler



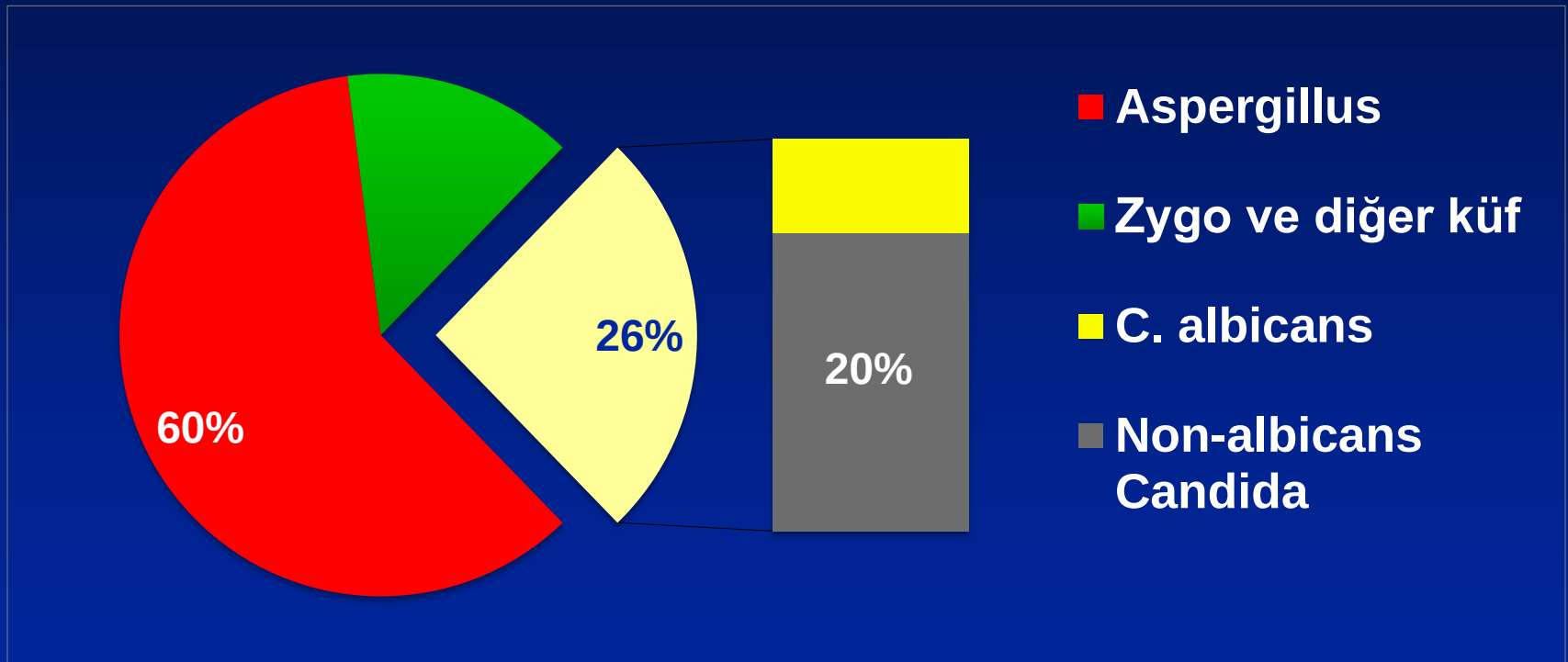
- Non-myeloablative “*conditioning*”
- Periferik kök hücre kullanımı
- Erken tanı

Erişikin Kök Hücre Nakli Yapılan Hastalarda İnvaziv Fungal İnfeksiyonlar

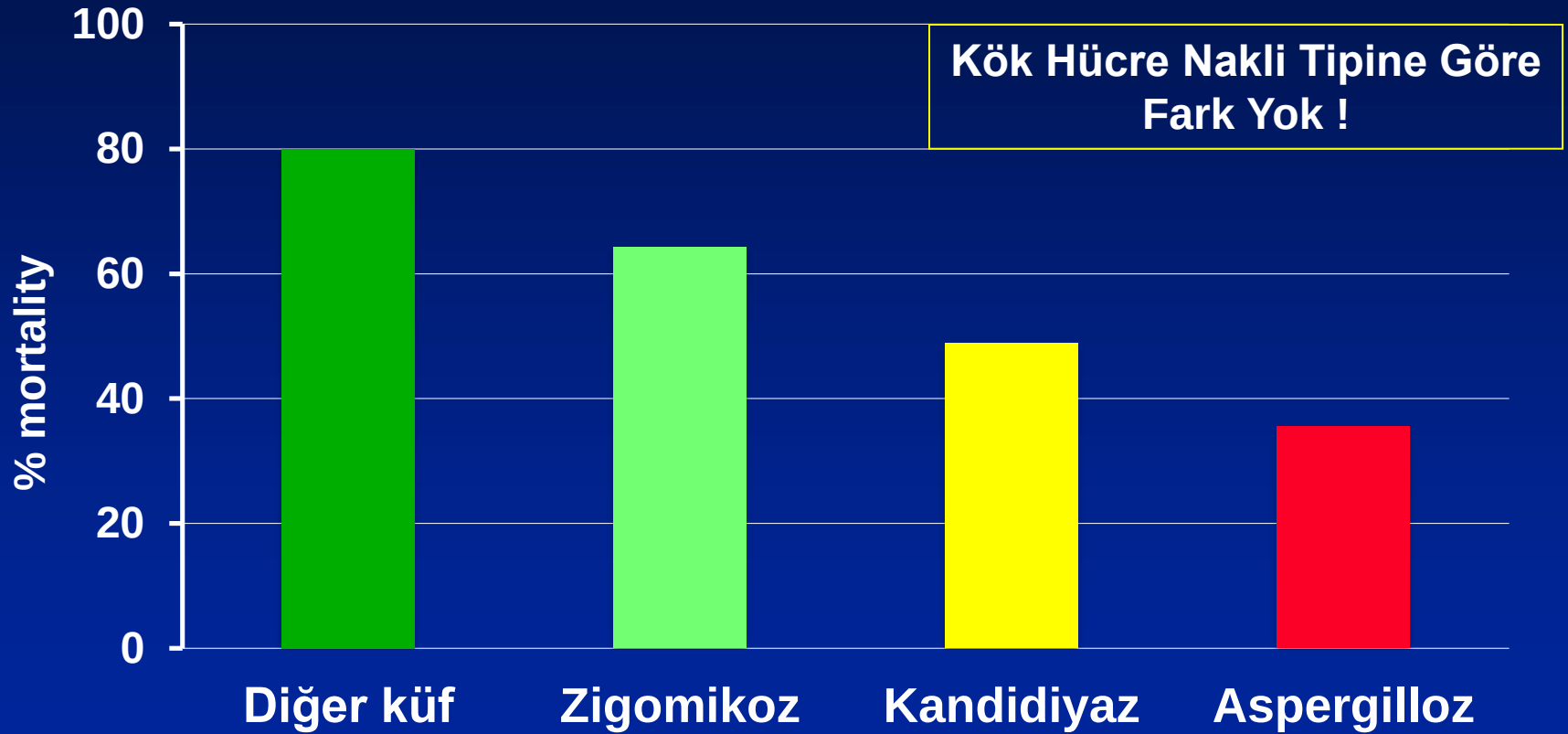
‘PATH Alliance Registry’

- **Kuzey Amerika’da 16 merkezde 234 hastada 250 IFI**
 - **%69 allojeneik**
 - **%31 otolog**
 - **IFI dağılımı**
 - **6 ve 12. haftalarda sağkalım**

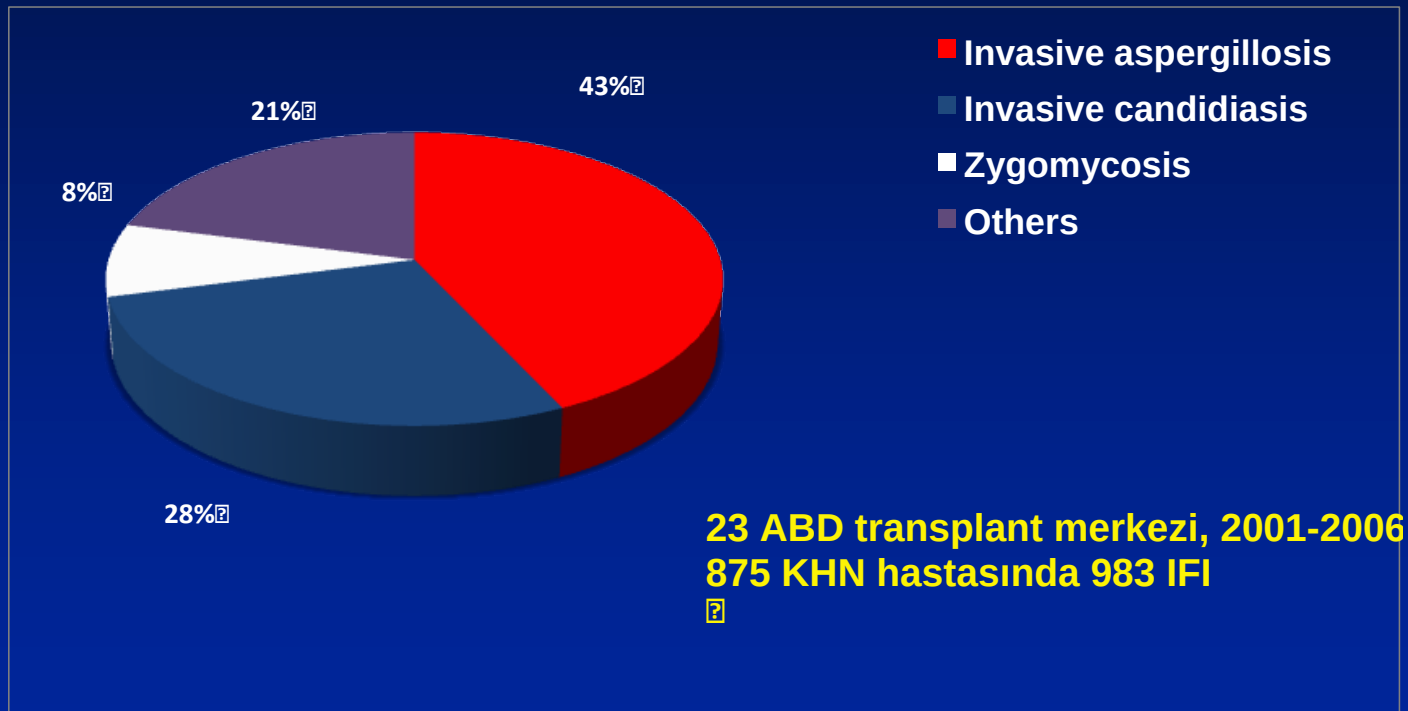
İnvaziv Fungal İnfeksiyon Dağılımı



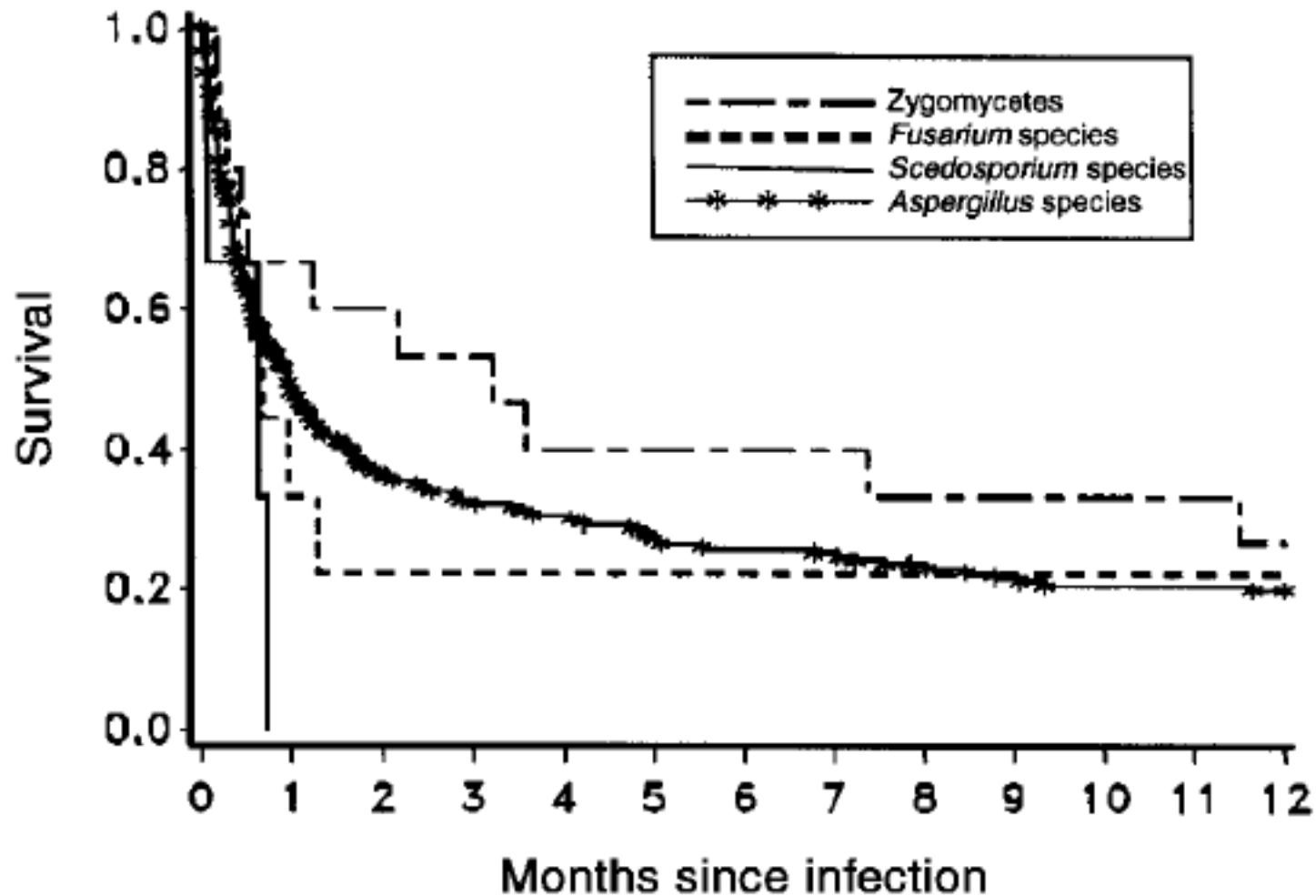
12. Haftada Mortalite



Kök Hücre Alıcılarında IFI TRANSNET Veritabanı



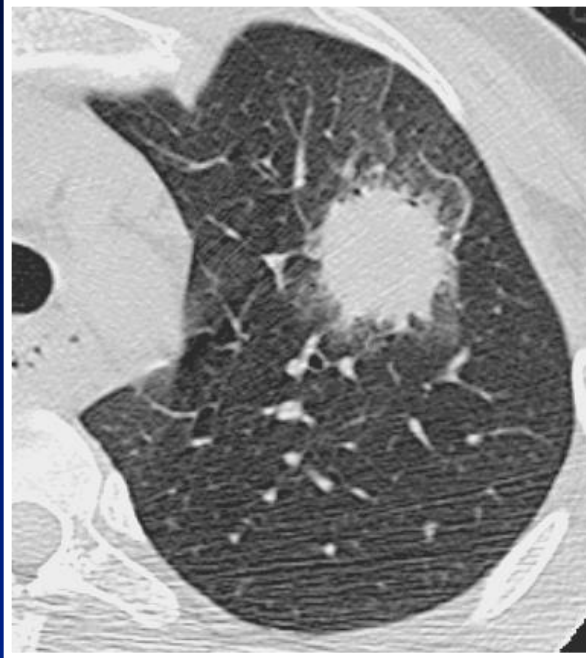
1 Yıllık Sağkalım



Standart Tanı Yöntemlerinin Duyarlılığı

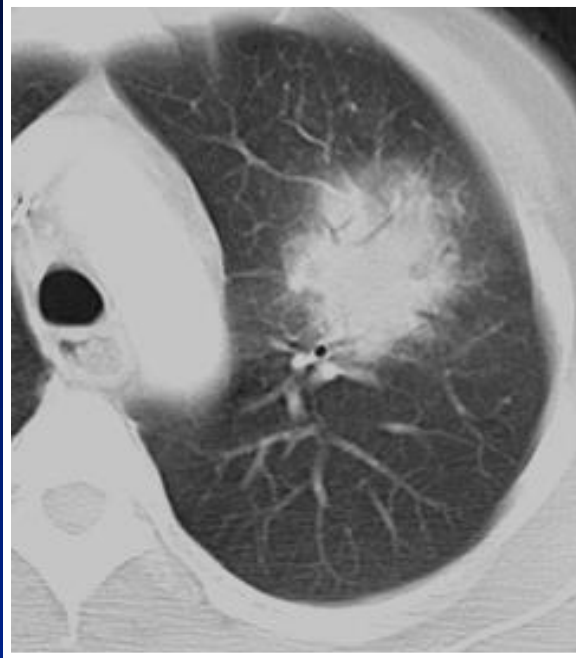
İnf. bölgesi	İşlem	% yapılma sıklığı	% duyarlılık
Pulmoner	Akciğer filmi	98	77
	BAL kültürü	38	62
	Balgam	72	58
	Nasal sürüntü	56	32
	Biyopsi	18	87
Serebral	Serebral BT	65	88
	Biyopsi	8	66
Sino-nasal	Kranial CT	50	86
	Nasal sürüntü	71	85
	Biyopsi	19	100

Akciğer BT



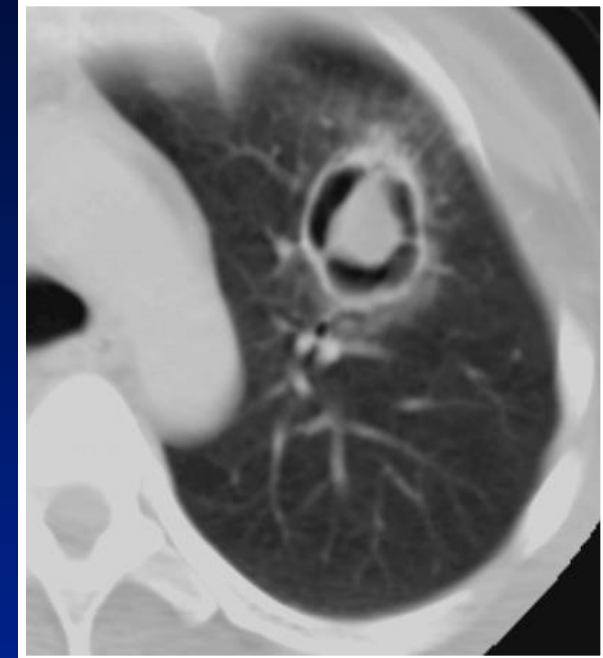
Halo belirtisi

G0	96%
G3	68%
G7	22%
G14	19%



Non-spesifik konsolidasyon

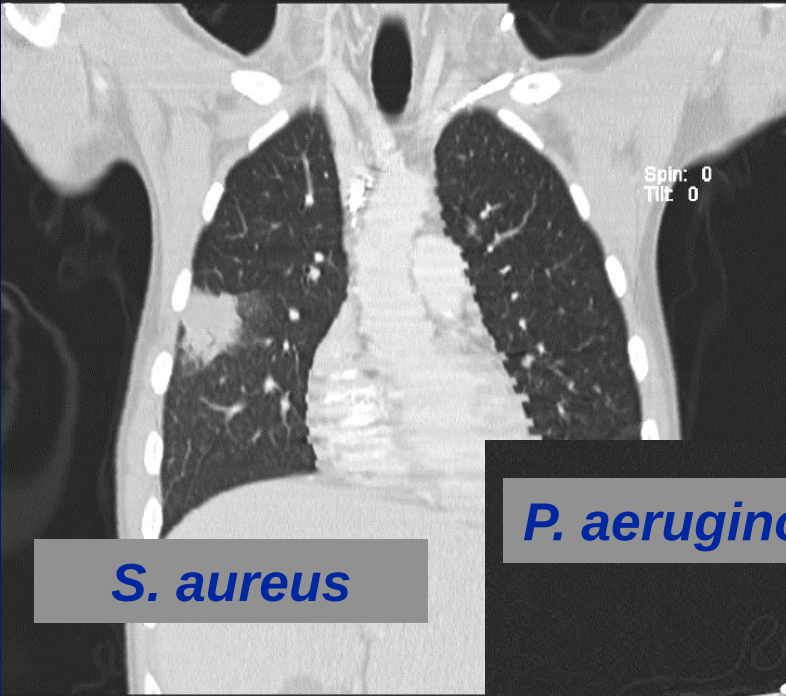
G0	
G3	31%
G7	50%
G14	18%



Hava hilal belirtisi

G0	0%
G3	8%
G7	28%
G14	63%

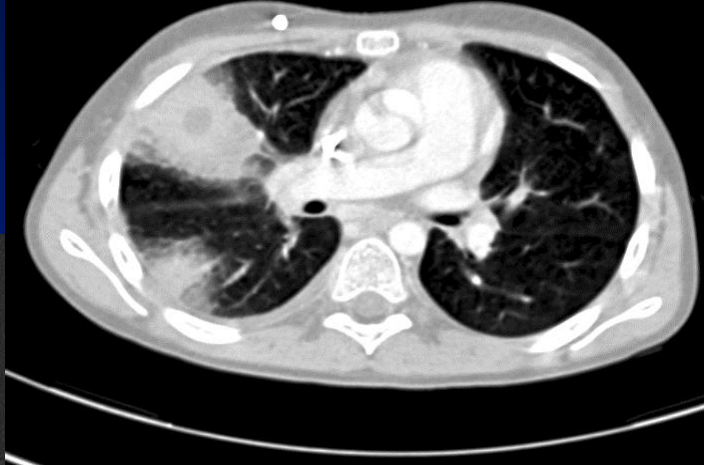
Halo Belirtisinin Özgüllüğü



P. aeruginosa



Pulmoner nokardiyoz



2013 Update of the ECIL Guidelines for Antifungal Therapy in Leukemia Patients

Invasive aspergillosis

Livio Pagano, Samir Agrawal, Andreas Groll

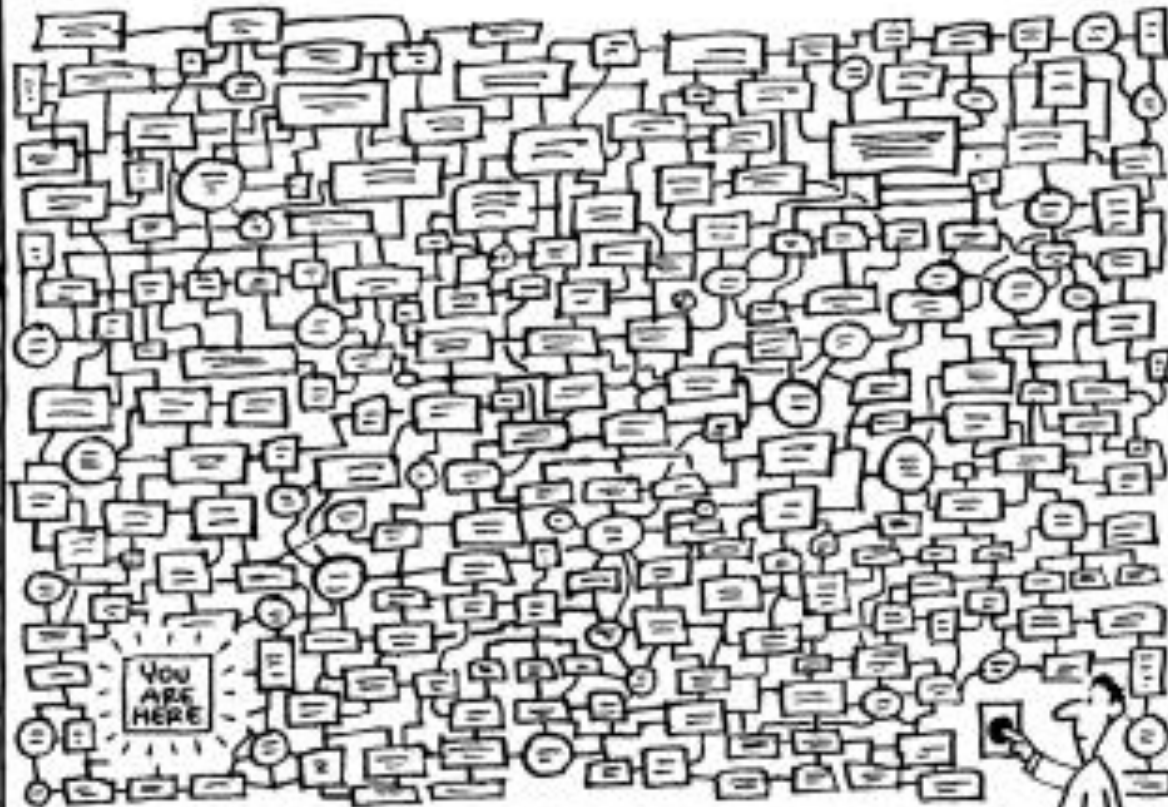
İnvaziv Aspergillozis'te Cerrahi Tedavi

- **Aşağıdaki durumlarda önerilir CIII**
 - **Büyük damara bitişik lezyon**
 - **Tek lezyon nedeniyle hemoptizi**
 - **Lokalize ekstrapulmoner lezyon**
 - **SSS lezyonları dahil**
 - **Olguya göre değerlendirme yapılmalı**

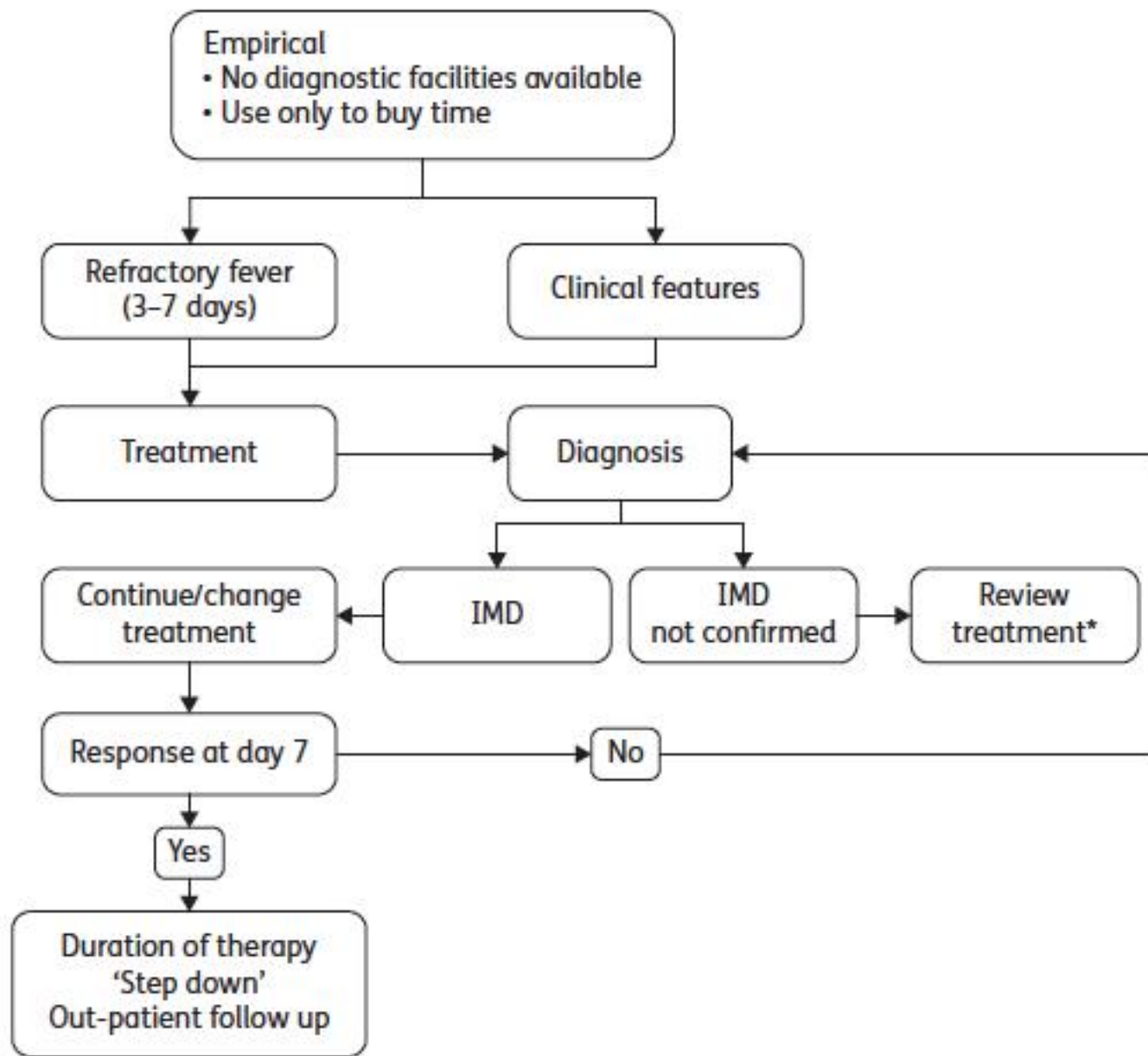
Yanıt Bekleyen Sorular

- **Tedavi süresi**
- **İlaç serum düzeyi tayini**
 - Özellikle azol türevlerinde tedavi başarısızlığı ve yan etki durumlarında
- **İn vitro duyarlılık**
 - Filamentöz funguslar rutin test edilmez
 - Duyarlılık ve etkinlik arasında ilişki yok
 - Tür düzeyinde identifikasyon CII

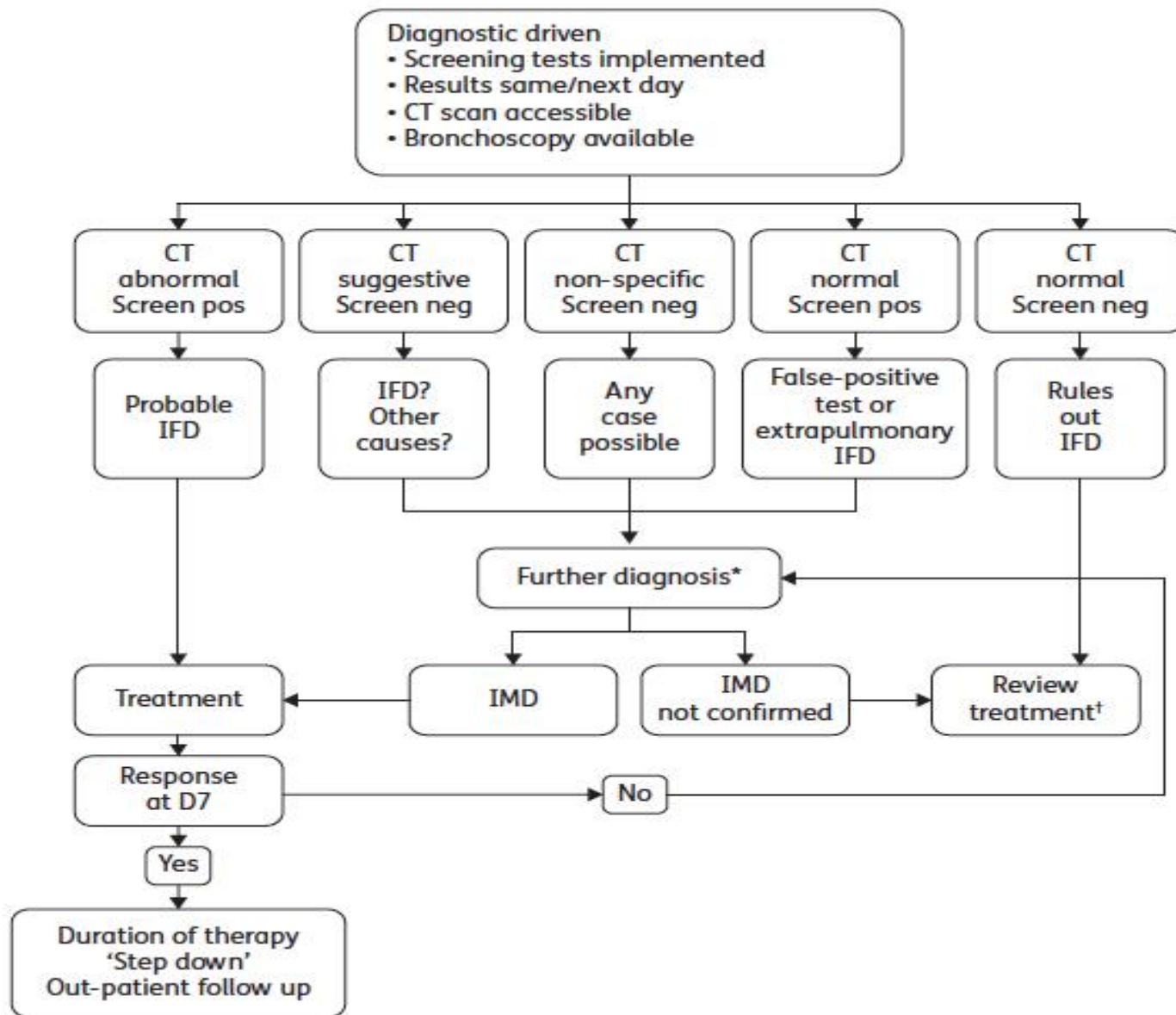
THE GRAND SCHEME OF THINGS:



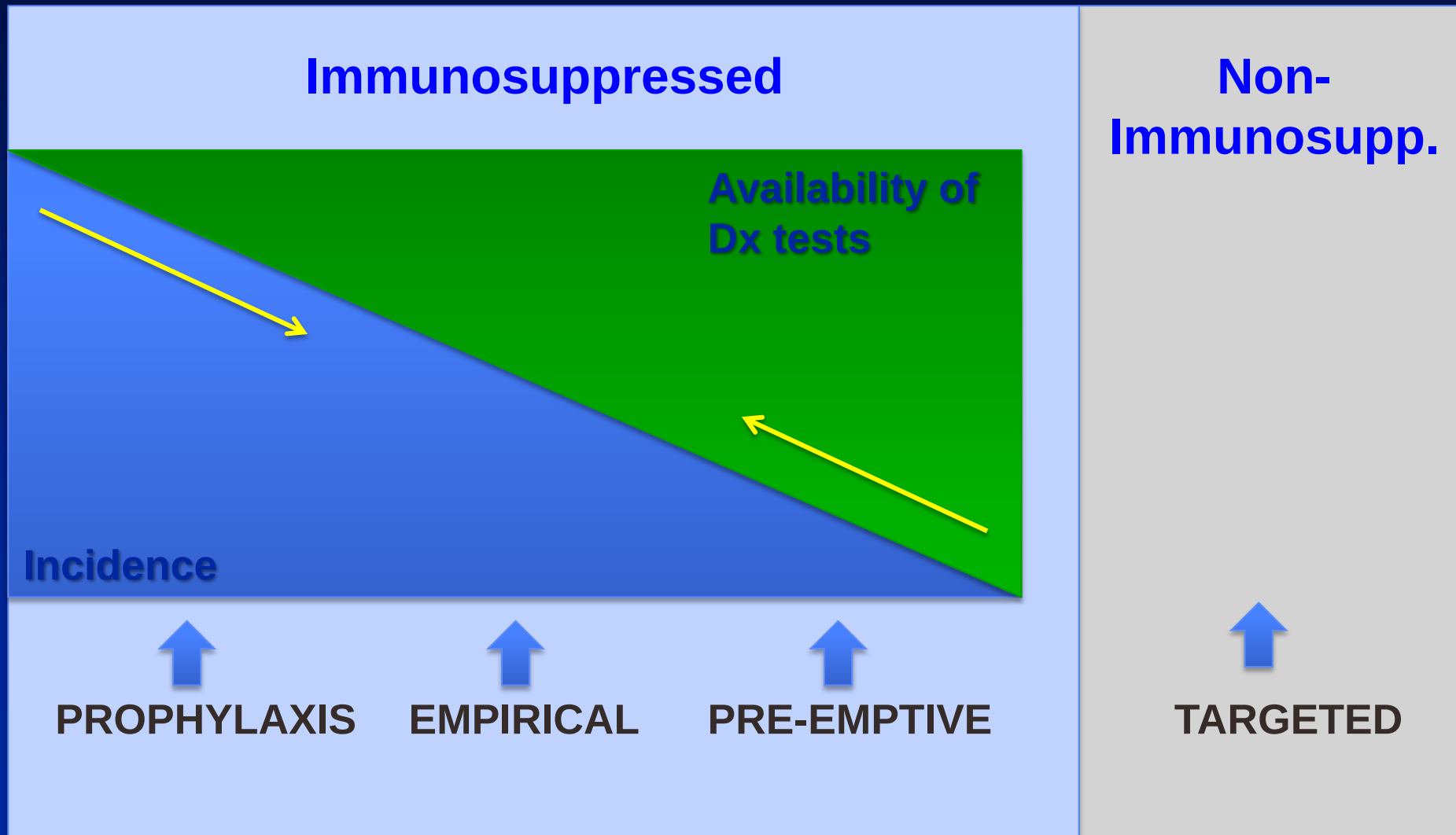
Empirical Antifungal Therapy Integrated Care Pathway



Diagnostic Driven Antifungal Therapy Integrated Care Pathway



Which Strategy to Choose?



Teşekkürler...