Yoğun Bakım Hastalarında

İnvazif Fungal İnfeksiyonların Erken Tedavisi

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Koç Üniversitesi Tıp Fakültesi

İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

10.03.2022

Sunum Planı

- **İnvazif Fungal İnfeksiyonlar**
  - Değişen epidemiyoloji
  - **YBÜ** ve diğer risk faktörleri
- **Antifungallere direnç**
  - Antigungal yönetim
  - Erken tedavi
- **İlaç etkileşimleri** ve biyoyararlanım
- Soru & Katkı

2020 First WHO Fungal Priority Pathogen List

- ✓ *Candida auris*
- ✓ Azole-resistant *Candida spp*.
- ✓ Azole-resistant *Aspergillus fumigatus*
- ✓ *Cryptococcus neoformans* (& *C. gattii*)
- ✓ *Pneumocystis jirovecii*
- ✓ *Mucorales*
- ✓ Potentially Histoplasmosis

all of global **public health importance** based on **limitations of treatment** options due to **resistance** and/or **treatability issues**

WHO Antifungal Expert Group Priority Fungal Pathogens. Report. Geneva: WHO; 2020.

İFİ Güncel Epidemiyoloji

ve Risk Faktörleri

Biomarkers in early treatment of invasive candidiasis

Hospital Practice. 2018; 46:5, 239-42.

Anahita Rouze, Julien Poissy, Boualem Sendid & Saad Nseir

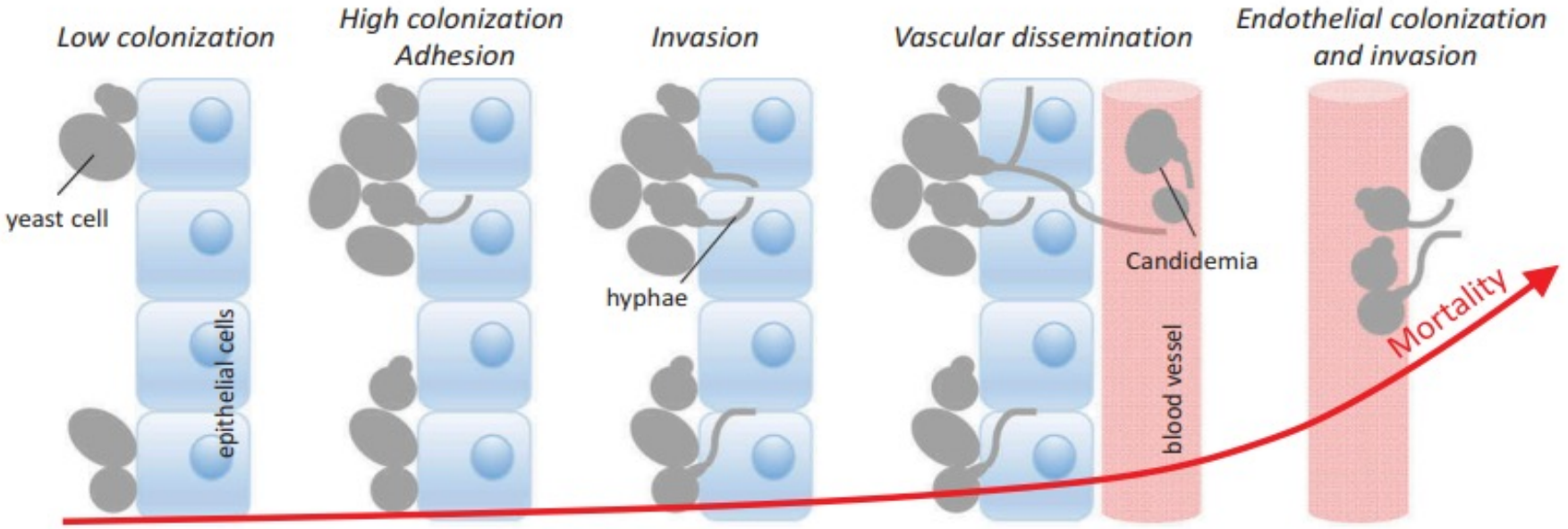
Monday morning, phone call from the lab, 'Blood cultures you collected Friday evening from Mrs…..have turned **positive for yeasts**! Is he on **antifungal**?' Such a common scene in intensive care units (ICU). . . 'Not yet.

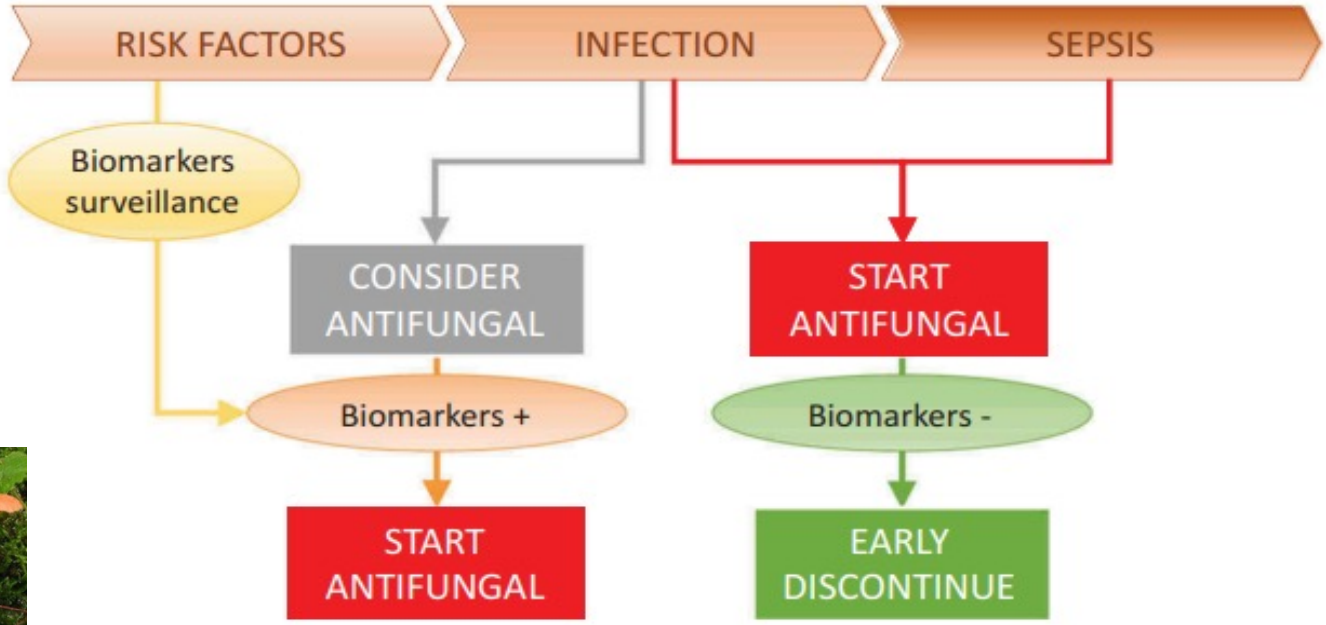
Artan kandidemi insidansı;

- **Geniş spektrumlu antibiyotik** tedavisinin artan kullanımı
- Bağışıklığı baskılanmış hastaların artan insidansı
- **YBÜ**'de invazif prosedürlerin çoğalması

Kandidemi kritik hastalarda **ölüm oranı %40**

Septik şok durumunda **%80'e** yükselir





Hospital Practice. 2018; 46:5, 239-242.

Table 1. Prospective interventional studies assessing biomarker-driven management strategies for triggering [11,15–17] or discontinuing [19,20] antifungal therapy in patients at risk for invasive candidiasis.

Reference	Study design	Population	Biomarker-driven strategy	Results (IC, AFT)	Mortality
Akamatsu, 2007 [15]	Observational Single-center	180 liver transplant recipients	BDG surveillance x1/week > 40 pg/ml, confirmed Start of AFT (fluconazole + trimethoprim-sulfamethoxazole)	IFI 24/180, including 14 IC AFT 40/180	Mortality 1/180
Namikawa, 2013 [16]	Randomized Single-center	81 surgical patients ≥70 years gastric cancer surgery	BDG screening once on postoperative day 1 If ≥11 pg/ml (26 patients) - Intervention:Start of AFT (fluconazole)	- Intervention: IC 0/13 - Control: IC 1/13	Mortality 0/81 Intervention: reduced fever on postoperative day 8
Hanson, 2012 [11]	Randomiz Single-ce				
Ostrosky-Zeichner, 2014 [17]	Randomiz Double-B Multicent				Mortality - Intervention: 25/117 - Control: 16/102
			Caspofungin - Control: Placebo in either situation	Control: IC 31/102*	
Nucci, 2016 [19]	Observational Multicenter	85 mixed ICU patients, receiving empirical AFT (anidulafungin), based on clinical prediction rules, and clinical/biological signs of infection	BDG screening, 3 consecutive days, after initiation of empirical AFT If ≥80 pg/ml, once; AFT ≥10 days If <80 pg/ml, three times; discontinuation of empirical AFT at day 4	- BDG positive: IC 7/64 - BDG negative: IC 0/21	Mortality - BDG positive: 34/64 - BDG negative: 9/21
Rouzé, 2017 [20]	Randomized Single-center	109 mixed ICU patients, receiving empirical AFT (any), based on clinical prediction rules, and clinical signs of infection	Determination of empirical AFT duration- Intervention: BDG, mannan, and anti-mannan based algorithm, measured at day 0 and day 4, possibly allowing early discontinuation of AFT at day 5 - Control: Standard care (14 days)	- IC: Intervention: 4/54 Control: 1/55 - Early stop of empirical AFT (<day 7) Intervention: 29/54 Control: 1/55*	Mortality - Intervention: 15/54 - Control: 15/55

*Kan kültüründen mantar türlerinin izolasyonundan **24 saat sonra uygun antifungal tedavinin ertelenmesinin**, kandidemili hastalarda **ölümün bağımsız bir belirleyicisi** olduğu gösterilmiştir.

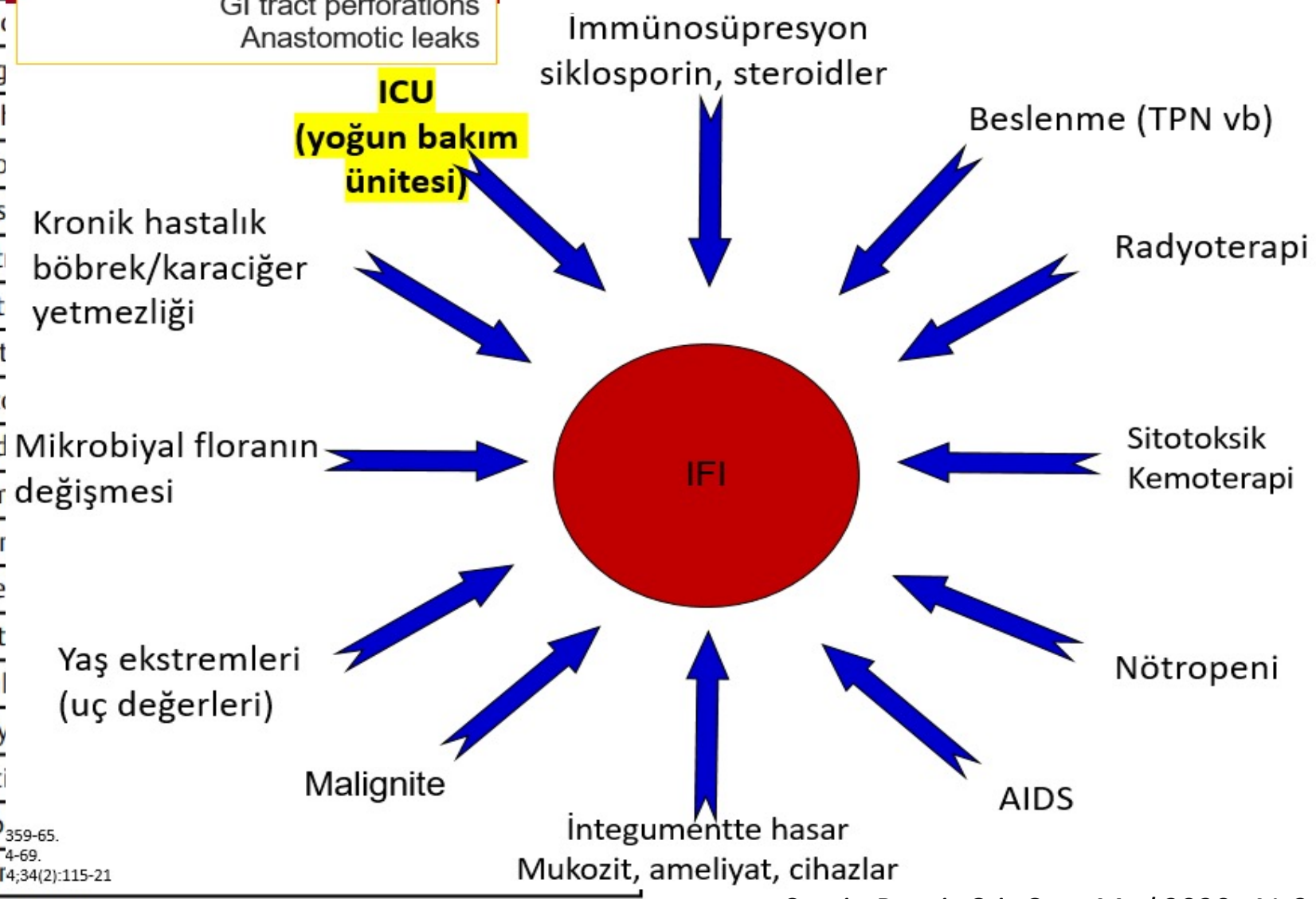
Hospital Practice. 2018; 46:5, 239-242.

Table 1 Risk factors for invasive candidiasis

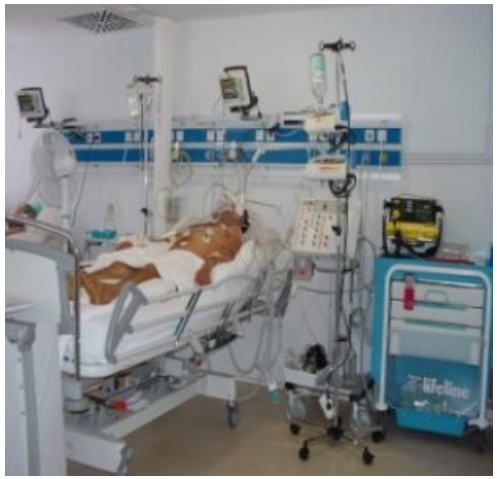
Mult
Broa
Criti
Long
Mech
Majo
Anas
Gast
Acut
Neut
Muco
Solid
Stem
Neor
Olde
Cent
Total
Dialy
Corti
Diab
IV dr

Central venous catheters
Broad-spectrum antibiotics
High APACHE scores
GI tract perforations
Anastomotic leaks

359-65.
4-69.
4;34(2):115-21



Semin Respir Crit Care Med 2020; 41:3–12.



YBÜ'de Ek Risk Faktörleri

- ✓ **Farmakokinetik değişkenlik,** tedavi başarısızlığına ve antifungal tedaviyle ilişkili **toksisitelere** önemli bir katkıda bulunur.
- ✓ **Kritik** hasta veya ciddi şekilde **bağışıklığı baskılanmış** hastalarda bir dizi **PK/PD** faktörü, **antifungal tedavinin etkinliğini** etkiler.

Age

Altered VD sepsis related

Weight (obesity)

Hypoalbuminemia

Altered renal function

Extracorporeal circuits (RT or ECMO)

Drug interactions

Lewis RE, Andes DR. *Curr Opin Infect Dis*. 2021 May 19

YBÜ *Candida* spp. dağılımı

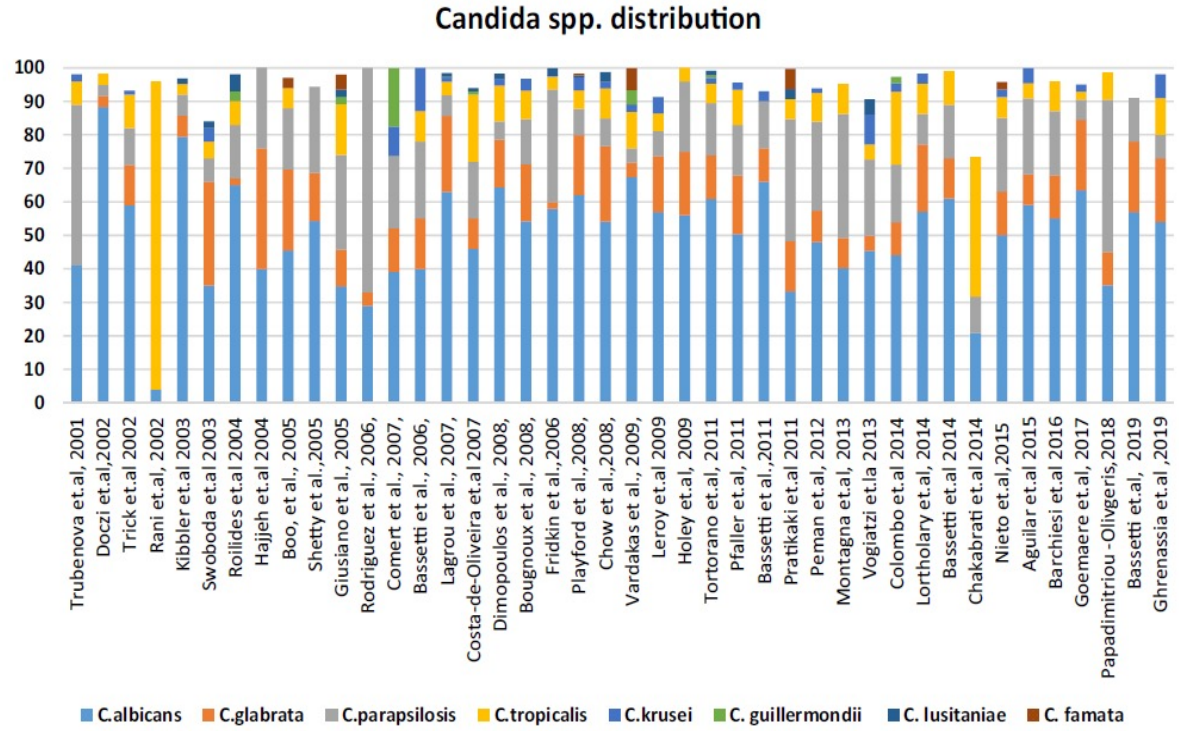
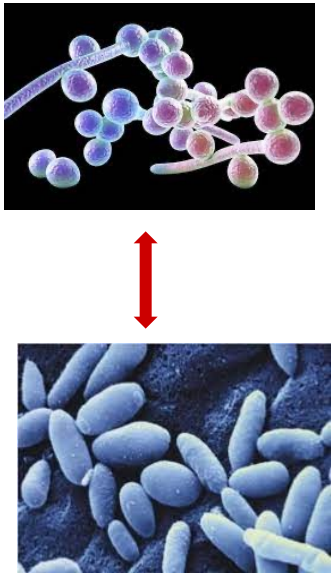


Fig. 1 Distribution of Candida spp. in 42 ICU studies [8, 35, 66, 69, 70, 72, 76–88, 90, 91, 94–97, 99, 100, 104, 133–145, 164]. *ICU* intensive care unit



YBÜ Epidemiolojik değişim

Time period	Albicans	Non-albicans	*p* (value)
2001–2010	3929/6957 (56.48%)	3028/6957 (43.52%)	<0.001
2011–2020	3258/6497 (50.15%)	3239/6497 (49.85%)	

Soulountsi V, Schizodimos T, Kotoulas SC. *Infection*. 2021;16.

Open Forum Infectious Diseases

MAJOR ARTICLE

Adam *et al*. *OFID*. 2021.

Trends of the Epidemiology of Candidemia in Switzerland: A 15-Year FUNGINOS Survey

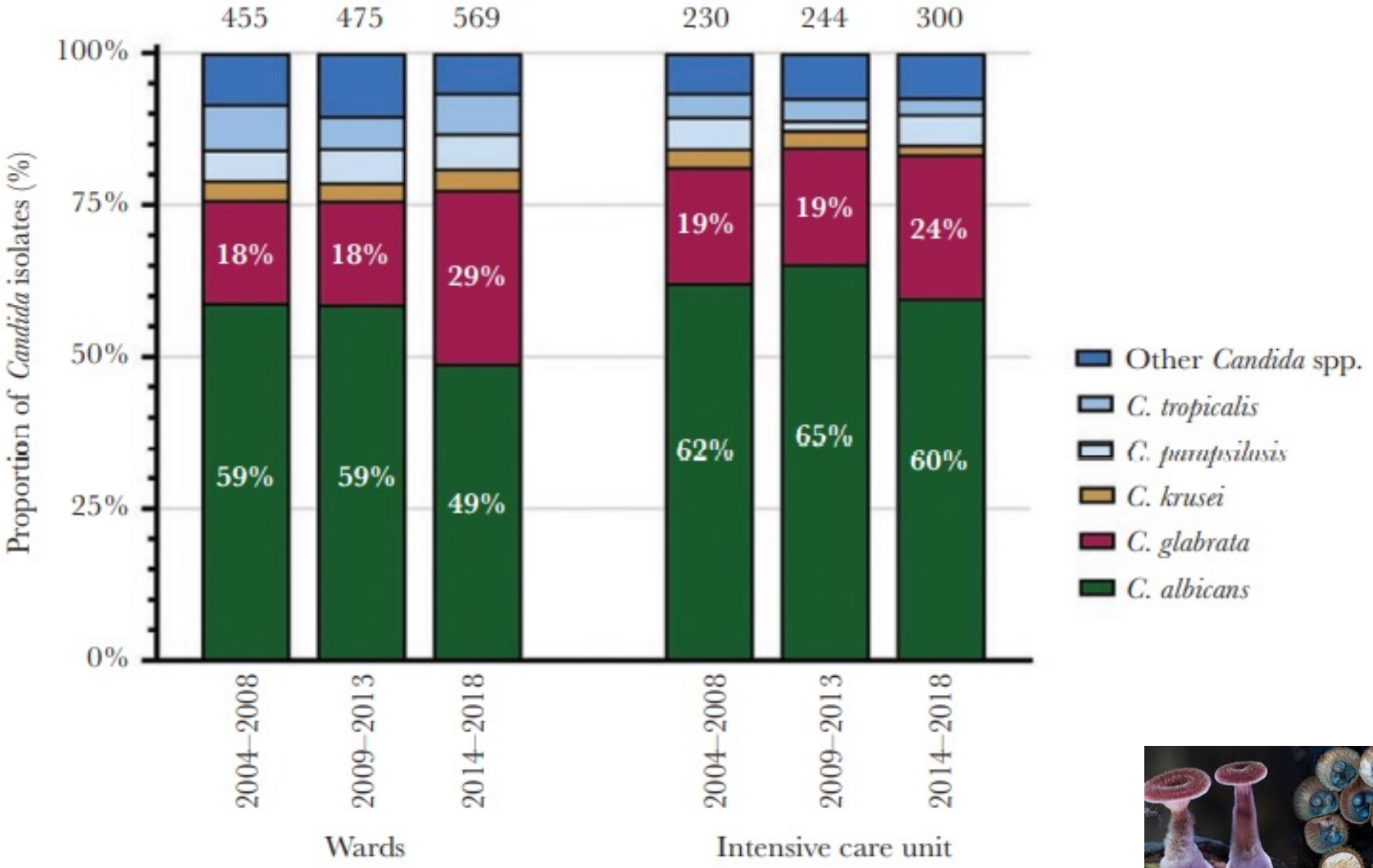
Kai-Manuel Adam,[1] Michael Osthoff,[1,2] Frédéric Lamoth,[3,4] Anna Conen,[5] Véronique Erard,[6] Katia Boggian,[7] Peter W. Schreiber,[8] Stefan Zimmerli,[9,10] Pierre-Yves Bochud,[3] Dionysios Neofytos,[11] Mapi Fleury,[12] Hans Fankhauser,[13] Daniel Goldenberger,[14] Konrad Mühlethaler,[9,10] Arnaud Riat,[15] Reinhard Zbinden,[16,*] Andreas Kronenberg,[10,*] Chantal Quiblier,[16,*] Oscar Marchetti,[3,17,a] and Nina Khanna[1,2,a]; the Fungal Infection Network of Switzerland (FUNGINOS)**

The Fungal Infection Network of Switzerland (**FUNGINOS**)

- 15 yıllık izlem **2004–2018,** (2004–2008, 2009–2013, 2014–2018)
- **2273 *Candida*** spp. kan izolatı
- Toplum kaynaklı kandidemi insidansı **2.96**'dan **4.20**/100 000 kişi (P = .022)
- SHİ kandidemi insidansı **0.86** to **0.99**/10 000 hasta-günü (P = .124).

Trends of the Epidemiology of Candidemia in Switzerland: A 15-Year FUNGINOS Survey

Adam *et al*. *OFID*. 2021.



Susceptibility of *Candida* Bloodstream Isolates to Antifungal Drugs According to CLSI Document M60-Ed2

Species	R or Non-WT**		
	2004–2008	2009–2013	2014–2018
Candida albicans			
Fluconazole	1%	1%	0%
Voriconazole	0%	1%	0%
Posaconazole	1%**	2%**	4%**
Caspofungin			
Amphotericin B			
Anidulafungin			
Micafungin			
Candida glabrata			
Fluconazole	0%	7%	4%
Voriconazole	0%	0%	2%
Posaconazole	0%**	3%**	2.5%**
Caspofungin	0%	0%	0%
Amphotericin B	0%**	0%**	2.5%**
Anidulafungin	-[a]	0%	0%
Micafungin	-[a]	0%	0%
Candida tropicalis			
Fluconazole	5%	12%	11%
Voriconazole	2%	12%	9%
Posaconazole	25%**	30%**	26%**
Caspofungin	0%	3%	0%

- **Sonuç olarak;**
- Son 2 dekatta ***C.glabrata*** ilişkili kandidemi artmış (kan dolaşımı izolatlarının **dörtte biri)**
- Küf tedavisinde **aktif triazollerin** daha fazla kullanılması sonucu ortaya çıkmış olabilir
- **Antifungal direnç değişimine** bağlı antifungal yöntiminde klavuzlar güncellenmeli

Adam *et al*. *OFID*. 2021.

RESEARCH ARTICLE

Candidemia in intensive care units over nine years at a large Italian university hospital: Comparison with other wards

Sara Mazzanti[1,2], Lucia Brescini[1,2], Gianluca Morroni[1], Elena Orsetti[3], Antonella Pocognoli[4], Abele Donati[1,5], Elisabetta Cerutti[6], Christopher Munch[7], Roberto Montalti[8], Francesco Barchiesi[1,9]*

İtalya'dan, 980 yataklı, **5 YBÜ**'si olan hastane

Rretrospektif, gözlemsel çalışma **Ocak 2010- Aralık 2018**

PLoS ONE. 2021;16: e0252165.

Table 1. Demographic and clinical characteristics of patients included in the study.

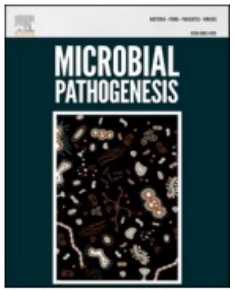
Characteristics	All patients	ICU	non-ICU
	n = 505	n = 188	n = 317
Male sex, *n (%)*	313 (62)	116 (62)	197 (62)
Age, median (IQR) [b]	70 (60–77)	71 (60–77)	70 (60–77)
Chronic pulmonary diseases, *n (%)* [c]	74 (15)	40 (21)	34 (11)
Hematological malignancy, *n (%)*	28 (6)	6 (3)	22 (7)
Cardiovascular diseases, *n (%)* [d]	284 (56)	134 (71)	150 (47)
Neurological diseases, *n (%)* [e]	122 (24)	51 (27)	71 (22)
Gastrointestinal diseases, *n (%)* [f]	132 (26)	39 (21)	93 (29)
Diabetes mellitus, *n (%)*	101 (20)	48 (26)	53 (17)
Candida species			
Candida albicans, n (%)	256 (51)	98 (52)	158 (50)
Candida parapsilosis, n (%)	129 (26)	45 (24)	84 (27)
Candida tropicalis, n (%)	44 (9)	13 (7)	31 (10)
Candida glabrata, n (%)	50 (10)	26 (14)	24 (8)
Other *Candida* species, *n (%)* [l]	26 (5)	6 (3)	20 (6)
Appropriate antifungal therapy, *n (%)* [m]	271 (54)	91 (49)	180 (57)
Primary antifungal therapy			
Azoles, *n (%)*	221 (45)	79 (42)	142 (45)
Echinocandins, *n (%)*	153 (30)	48 (25)	105 (33)
No treatment, *n (%)*	123 (25)	59 (32)	64 (20)
7-days mortality, *n(%)*	71 (14)	35 (19)	36 (11)
30-days mortality, *n(%)*	150 (30)	77 (41)	73 (23)

Table 4. Risk factors associated with 7- and 30-day mortality in ICU patients with candidemia analyzed by logistic re

Factors		7-days mortality			30-days mortality
	Hazard ratio	CI 95%		*p* value	Hazard ratio
		Lower limit	Upper limit		
Cardiovascular surgery	-	-	-	-	1.985
Septic shock	3.583	1.510	8.501	0.004	2.465
Acute kidney failure	4.441	1.645	11.988	0.003	2.196
Polmunary embolism	6.492	1.226	34.365	0.028	-
Primary therapy with azoles	1.752	0.576	5.327	0.323	-
No antifungal therapy	4.072	1.704	9.732	0.002	-

At multivariate analysis, factors associated with **increased risk of death** were **septic shock**, **acute kidney failure**, **pulmonary embolism** and **lack of antifungal therapy**

PLoS ONE. 2021;16: e0252165.



Distribution of invasive fungal infections: Molecular epidemiology, etiology, clinical conditions, diagnosis and risk factors: A 3-year experience with 490 patients under intensive care

Zeinab Borjian Boroujeni [a], Sina Shamsaei [b], Mohammad Yarahmadi [c], Muhammad Ibrahim Getso [d], Alireza Salimi Khorashad [e], Leila Haghighi [b], Vahid Raissi [a,c,**], Mahdi Zareei [a], Anita Saleh Mohammadzade [f], Vahid Moqarabzadeh [g], Ameneh Soleimani [h], Farid Raeisi [i], Moein Mohseni [f], Maedeh Sadat Mohseni [j], Omid Raiesi [k,*]

Çalışmaya **1477 YBÜ** hastası alınmış

Bunlardan **490 İFİ**

✓*Candida* spp. %68.8

✓*Aspergillus* spp. %22

✓*Zygomycetes* spp. %4.3

Species-specific distribution of the etiology of systemic fungal infections.

Fungus	No. of patients (%)			P-value
	2016 (n = 609)	2017 (n = 456)	2018 (n = 412)	
Actinomyces	3 (0.5)	1 (0.22)	0 (0)	0.089
Alternaria Alternata	1 (0.16)	1 (0.22)	0 (0)	0.7857
Aspergillus Clavatus	2 (0.33)	0 (0)	0 (0)	0.1431
Aspergillus Flavus	20 (3.3)	23 (5.1)	31 (7.52)	**0.0001***
Aspergillus Fumigatus	4 (0.65)	6 (1.3)	8 (1.94)	**0.0001***
Aspergillus Niger	1 (0.16)	3 (0.65)	4 (0.97)	**0.0001***
Aspergillus Terreus	2 (0.32)	3 (0.65)	0 (0)	0.2464
Aspergillus Tubigensis	0 (0)	1 (0.22)	0 (0)	0.1444
Candida Albicans	46 (7.6)	45 (9.8)	17 (4.1)	0.3251
Candida glabrata	18 (2.9)	25 (5.4)	35 (8.5)	**0.0001***
Candida parapsilosis	15 (2.4)	19 (4.2)	19 (4.6)	**0.0001***
Candida tropicalis	9 (1.4)	11 (2.4)	15 (3.6)	**0.0001***
Candida dubliniensis	9 (1.4)	8 (1.7)	5 (1.2)	0.3330
Candida kefyr	5 (0.8)	4 (0.87)	3 (0.72)	0.7420
Candida krusei	3 (0.49)	4 (0.87)	4 (0.97)	**0.0001***
Candida guilliermondii	4 (0.65)	5 (1.1)	2 (0.48)	0.4857
Candida lusitaniae	0 (0)	2 (0.32)	3 (0.72)	**0.0001***
Candida intermedia	2 (0.33)	0 (0)	0 (0)	0.2887
Cryptococcus spp	1 (0.16)	1 (0.22)	1 (0.24)	0.0677
Fusarium spp	0 (0)	1 (0.22)	3 (0.72)	**0.0001***

Veri Sınıflandırma Tipi: Genel / General

First Report of Candidemia Clonal Outbreak Caused by Emerging Fluconazole-Resistant *Candida parapsilosis* Isolates Harboring Y132F and/or Y132F+K143R in Turkey

Amir Arastehfar,[a] Farnaz Daneshnia,[b] Suleyha Hilmioğlu-Polat,[c] Wenjie Fang,[d,e] Melike Yaşar,[c] Furkan Polat,[c] Dilek Yeşim Metin,[c] Petra Rigole,[f] Tom Coenye,[f] Macit Ilkit,[g] Weihua Pan,[d,e] Wanqing Liao,[d,e] Ferry Hagen,[b,h] Markus Kostrzewa,[i] David S. Perlin,[a] Cornelia Lass-Flörl,[j] Teun Boekhout[b,k]

The **increased rate of invasive candidiasis with non-albicans** agents highlights a **new perspective in the epidemiology** and **treatment** of invasive fungal infections.

In total, **26.4%** of the isolates were **FLZR** (n 60)

among them, **31.6%** (n 19) were **cross-resistant** to **VRZ**

Antimicrob Agents Chemother. 2020; 64:e01001-20.

Clonal Candidemia Outbreak by *Candida parapsilosis* Carrying Y132F in Turkey: Evolution of a Persisting Challenge

Amir Arastehfar[1†‡], Suleyha Hilmioğlu-Polat[2†‡], Farnaz Daneshnia[1†], Weihua Pan[3], Ahmed Hafez[4], Wenjie Fang[3†], Wanqing Liao[3], Zümrüt Şahbudak-Bal[5†], Dilek Yeşim Metin[2†], João N. de Almeida Júnior[6,7†], Macit Ilkit[8†], David S. Perlin[1*†] and Cornelia Lass-Flörl[9†]*

C. parapsilosis in Ege UH in **2019-2020**.

Toplam **58 *C. parapsilosis*** izolatı 47 hastanın kanından üretilmiş

Antifungal duyarlılıklar **CLSI** M60 protocol **Flukonazol** için **ERG11**

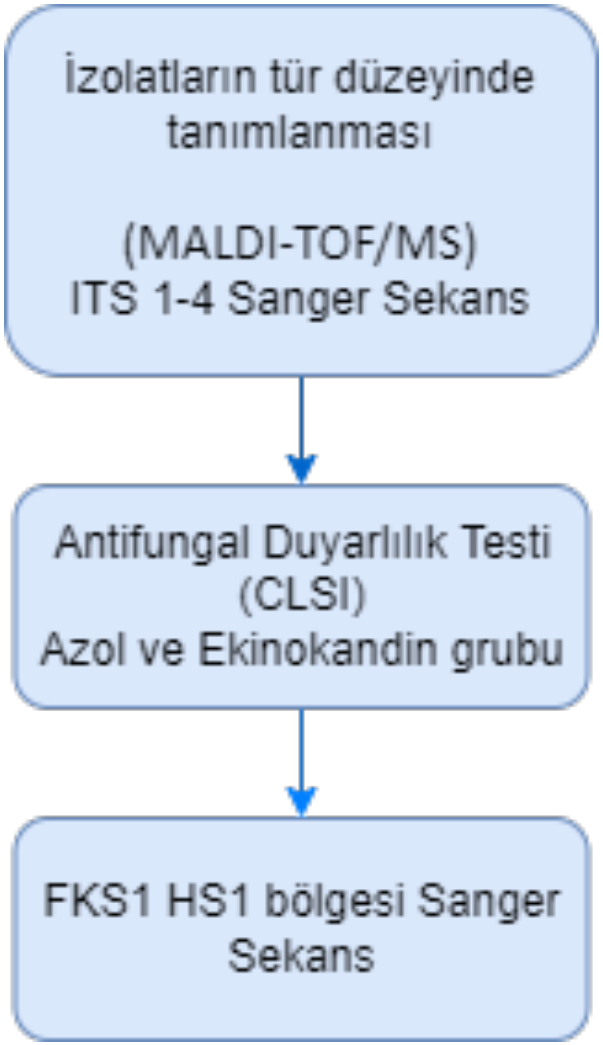
Ekinokandin için **HS1/HS2-FKS1** sekans bakılmış.

Overall **mortalite** hızı **%27.6**

frontiers in Cellular and Infection Microbiology April 2021 | Volume 11 | Article 676177

Koç Üniversitesi Hastanesi kandidemili hastalardaki *C.parapsilosis* suşlardaki antifungal duyarlılık

- **MALDI-TOF/MS** yöntemi ve
- **ITS1-4** bölgelerinin sekanslanmasıyla doğrulanan **2019- 2021 yılları** arasında hastaların **kan örneklerinden** izole edilen **34 adet *C.parapsilosis*** suşu incelendi.
- Amaç; hastanemizde **kan kültüründen** izole edilen ***C.parapsilosis*** izolatlarında ortaya çıkan **ekinokandin direncinin** altta yatan **moleküler mekanizmasının** aydınlatılmasıdır.



KUISCID yayımlanmamış veri

Koç Üniversitesi Hastanesi kandidemili hastalardaki *C.parapsilosis* suşlardaki antifungal duyarlılık

❖**Antifungal duyarlılık testi**;

Azol grubu → flukonazol, vorikonazol, posakonazol

Ekinokandin grubu → mikafungin, kaspofungin

❖Ekinokandin direnci **VITEK** otomatize sistemi (Biomerieux, Fransa) ve **Sensititre** "**yeast one**" (Thermo Fisher, Amerika Birleşik Devletleri) kullanılarak saptanmış, Standart Mikrodilüsyon yöntemi ile **CLSI** kılavuzlarına uygun olarak doğrulanmıştır.

Tablo: Antifungal Duyarlılık Test sonuçları **MIK_{50}**, **MIK_{90}** değerleri (Standart Mikrodilüsyon yöntemi ,**CLSI** kılavuzu)

Candida türü	Antifungal ilaç	MIK (µg/mL)		
		MIK_{50}	MIK_{90}	Aralık
Candida parapsilosis	FLU	64	>64	1 - >64
	POS	0.5	0.5	0.125 - 0.5
	VOR	16	>16	0.06 - >16
	MFG	>16	>16	2 – >16
	CFG	>16	>16	2 - >16

KUISCID yayımlanmamış veri

Koç Üniversitesi Hastanesi kandidemili hastalardaki *C.parapsilosis* suşlardaki antifungal duyarlılık

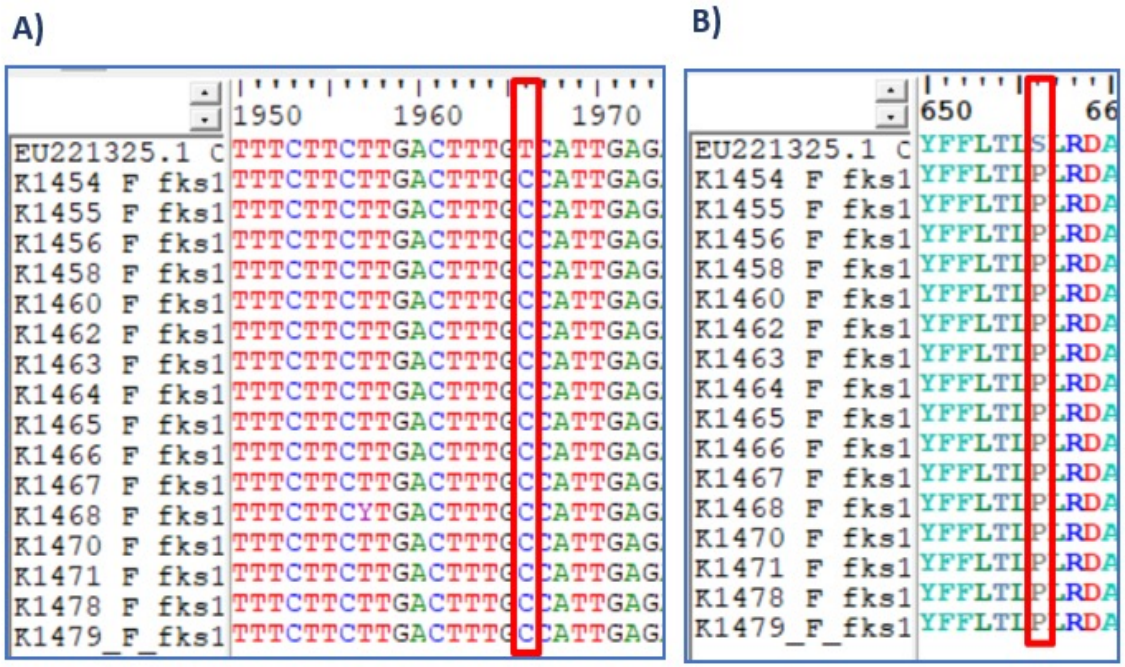
Sanger Sekans Analizleri

❖Mikrodilüsyon sonuçları;

mikafungin ve **kaspofungin**

MIK >16 ug/ml olan

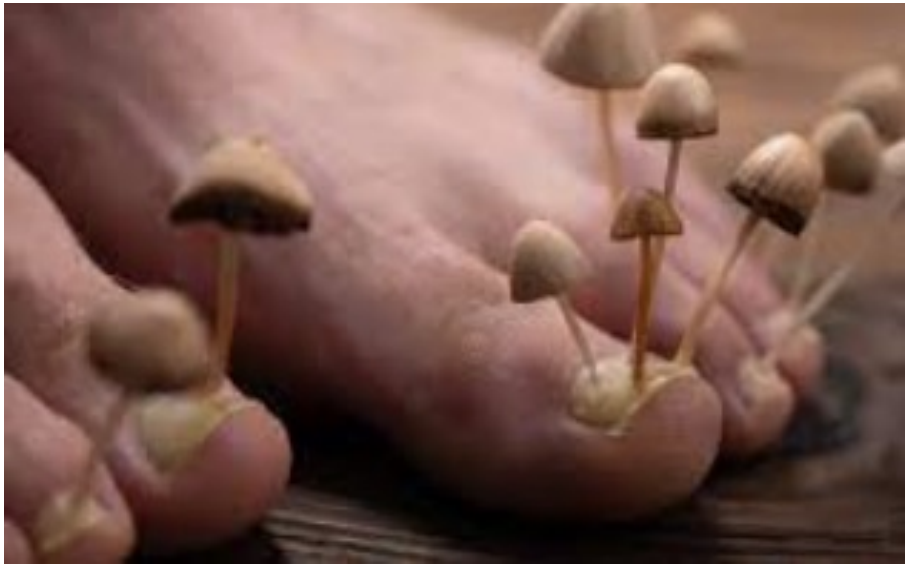
16 izolatın β 1,3 glukan sentazı kodlayan **FKS** geni **HS1** bölgesinde **Ser656 → Pro** mutasyonu saptanmıştır.



Figür: FKS1 geni HS1 **Ser656→Pro** mutasyonu, Bioedit (7.2)
A) Nükleotid gösterimi, **B)** Protein gösterimi

KUISCID yayımlanmamış veri

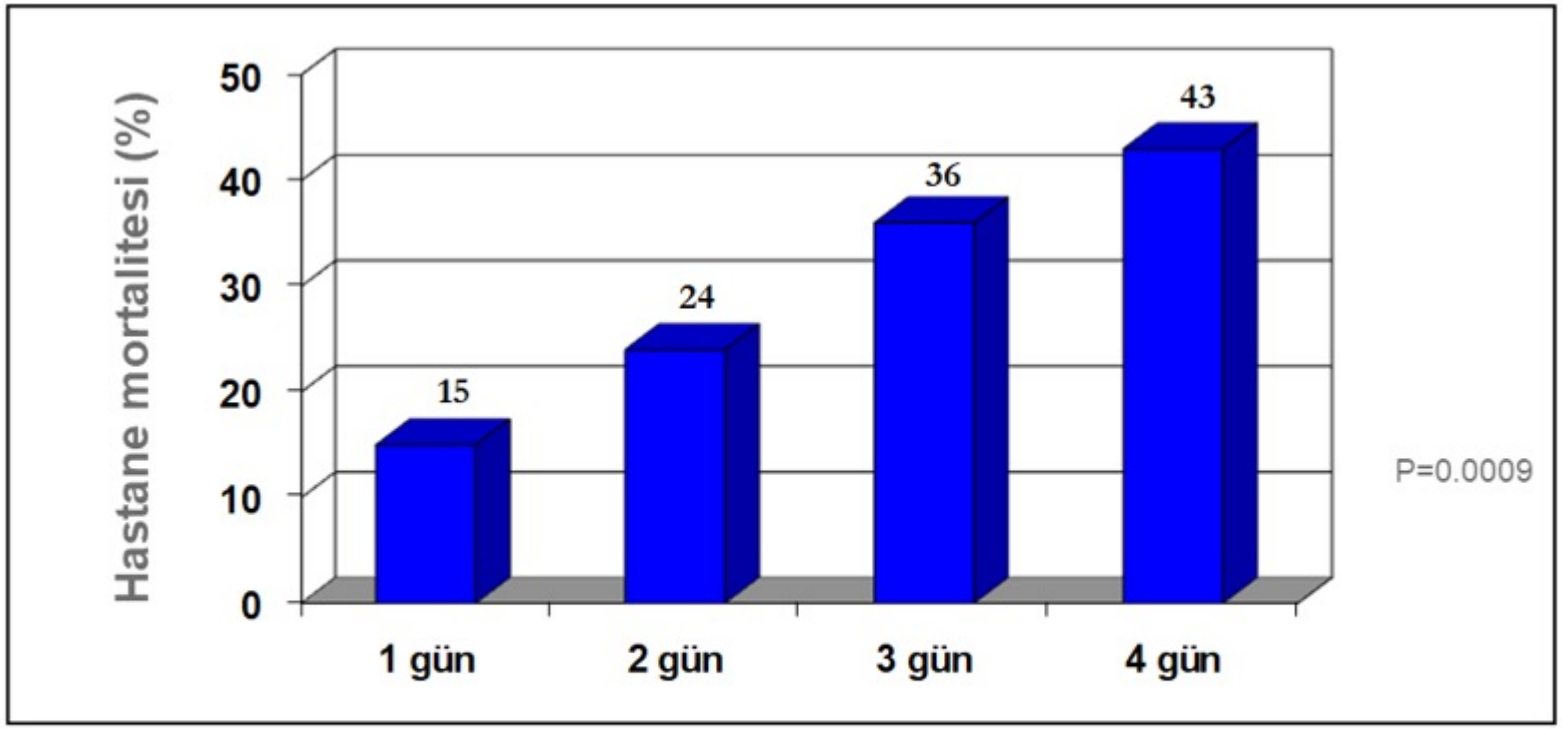
Erken Tedavide Sağkalım



Pozitif kültürler

Hedefe Yönelik

Tedaviye başlama gecikmesi



Garey KW et al. *CID* 2006; 43: 25-31.
Morrell et al. *AAC* 2005; 49: 3640-3645.

Zaragoza R, et al. *Ther Clin Risk Manag.* 2008; 4: 1261–80.

Multicenter Study > Clin Infect Dis. 2021 Oct 5;73(7):e1634-e1644. doi: 10.1093/cid/ciaa1298.

A National Strategy to Diagnose Coronavirus Disease 2019-Associated Invasive Fungal Disease in the Intensive Care Unit

P Lewis White [1], Rishi Dhillon [1], Alan Cordey [1], Harriet Hughes [1], Federica Faggian [1],

Çok merkezli, prospektif, kohort çalışma

YBÜ'de gelişen İFİ irdelenmiş (**İnfluenza** ve **COVID-19** ilişkili **PA**)

	All ICU patients (n=135)	Mycology positive (n=51)	Mycology negative (n=84)	P-value
Median Age (25^{th}/75^{th} percentile)	57 (48/64)	58 (50/69)	57 (47/63)	0·2305
Male/female	2.2/1	2/1	2.36/1	0·7038
Comorbidities (n/N)	112/131 (4 not available)	41/51	71/80 (4 not available)	0·2097
Comorbidities-listed	Diabetes mellitus: 38 Hypertension: 35 Chronic respiratory illness: 30 Obesity/Hyperlipidaemia: 27 Cardiac/Vascular disease: 18 Autoimmune/Inflammatory conditions: 18	Diabetes mellitus: 13 Hypertension: 16 Chronic respiratory illness: 14 Obesity/Hyperlipidaemia: 10 Cardiac/Vascular disease: 6 Autoimmune/Inflammatory conditions: 8	Diabetes mellitus: 25 Hypertension: 19 Chronic respiratory illness: 16 Obesity/Hyperlipidaemia: 17 Cardiac/Vascular disease: 12 Autoimmune/Inflammatory conditions: 10	0·5559 0·4185 0·3947 1·0000 0·7954 0·6083

Multicenter Study > Clin Infect Dis. 2021 Oct 5;73(7):e1634-e1644. doi: 10.1093/cid/ciaa1298.

A National Strategy to Diagnose Coronavirus Disease 2019-Associated Invasive Fungal Disease in the Intensive Care Unit

P Lewis White [1], Rishi Dhillon [1], Alan Cordey [1], Harriet Hughes [1], Federica [illegible]ggian [1],

YBÜ'de İFİ

- **İnsidansı %26.7**;
- Toplam **mortalit** **%31** (P: 0.03).

The use of **early antifungal therapy**, directed by strategic mycological testing infers a **survival benefit.**

Mortalite:

- ✓ **Antifungal** alanlarda **%38.5** & almayanlarda **%90** (P: 0.008)
- ✓ **Kortikosteroid** kullanımı (P: 0.007)
- ✓ **Kronik AC hastalığı** varlığı aspergillozda **mortaliteyi** ciddi **artırmakta** (P: 0.05)

YBÜ'de PK/PD faktörler: İlaç Etkileşimleri

Evaluation of Potential Drug–Drug Interactions in Adults in the Intensive Care Unit: A Systematic Review and Meta-Analysis

Mary Grace Fitzmaurice[1] · Adrian Wong[1,2] · Hannah Akerberg[1] · Simona Avramovska[1] · Pamela L. Smithburger[1,3] · Mitchell S. Buckley[4] · Sandra L. Kane-Gill[3,5]

Published online: 16 May 2019

Anahtar noktaları

- YBÜ hastalarının büyük çoğunluğu en az bir **ilaç-ilaç etkileşimine** maruz kalacaktır.
- Yaklaşık **altı hastadan biri klinik olarak** ilaç-ilaç etkileşimi yaşayacaktır.
- Klinik olarak ilgili **advers ilaç reaksiyonlarının %7 ila %44'ü** ilaç-ilaç etkileşimlerinden kaynaklanır.

European Review for Medical and Pharmacological Sciences 2021; 25: 5801-5806

Evaluation of potential drug-drug interactions in intensive care unit

M.S. DAGDELEN[1], D. GULEN[1], I. CEYLAN[2], N.K. GIRGIN[1]

[1]Anesthesiology and Reanimation, Bursa Uludag University Faculty of Medicine Hospital, Bursa, Turkey
[2]Anesthesiology and Reanimation, TC SBU Bursa Yüksek Ihtisas Training Hospital, Bursa, Turkey

- ✓ Retrospective cross-sectional study
- ✓ January 1, 2018, and December 31,2018
- ✓ 144 patients, 395 medication orders, **1776 pDDIs**.
- ✓ **23.5%** were **major** (n = 418), 71.4% were moderate , and 5.1% were minor.
- ✓ The majority of patients **(96.9%)** had at **least one pDDI**.

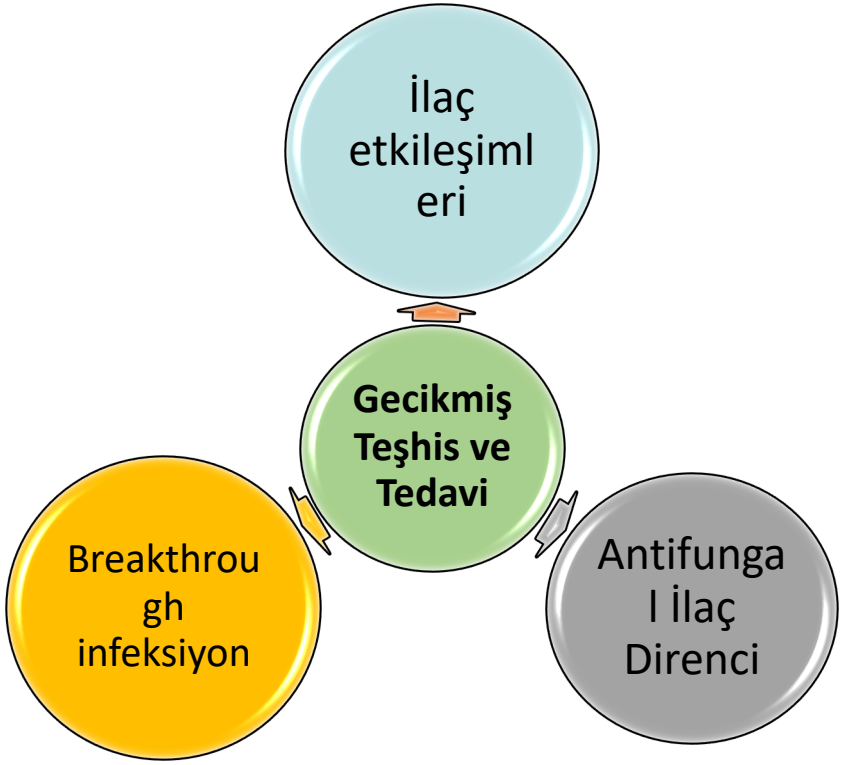
Fitzmaurice MG *Drug Safety* . 2019: 42:1035–44

REVIEW

Challenges and research priorities to progress the impact of antimicrobial stewardship

Matteo Bassetti MD, PhD[1,2,3], Daniele Roberto Giacobbe MD[2,3], Antonio Vena MD, PhD[1], Adrian Brink MMed[4]

[1]Infectious Diseases Clinic, Department of Medicine, University of Udine, Italy; [2]Infectious Diseases Unit, Ospedale Policlinico San Martino – IRCCS per l'Oncologia, University of Genoa, Largo R. Benzi, 10, 16132, Genoa, Italy; [3]Department of Health Sciences, DISSAL, University of Genoa, Genoa, Italy; [4]Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

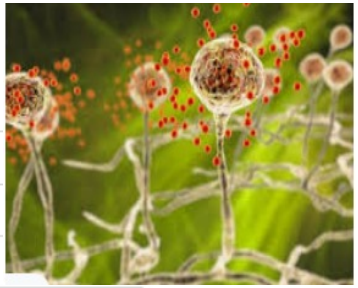


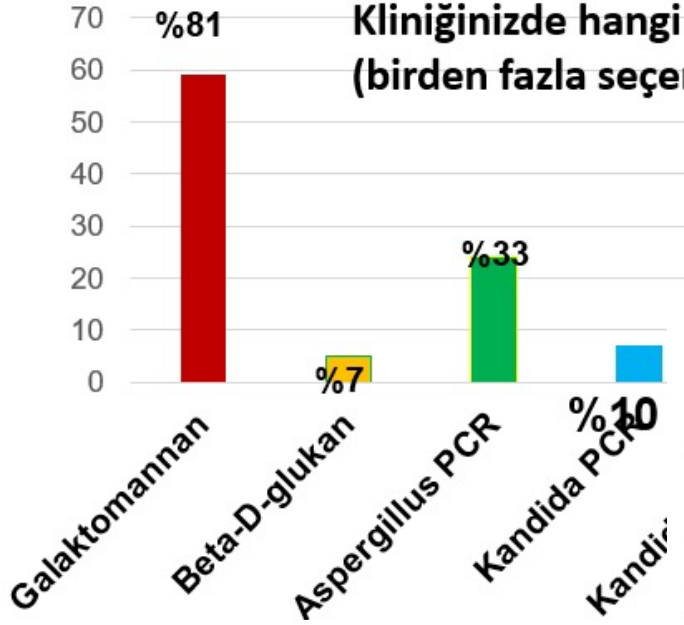
Rayens E. *Clin Infect Dis*. 2021: 20: ciab336.

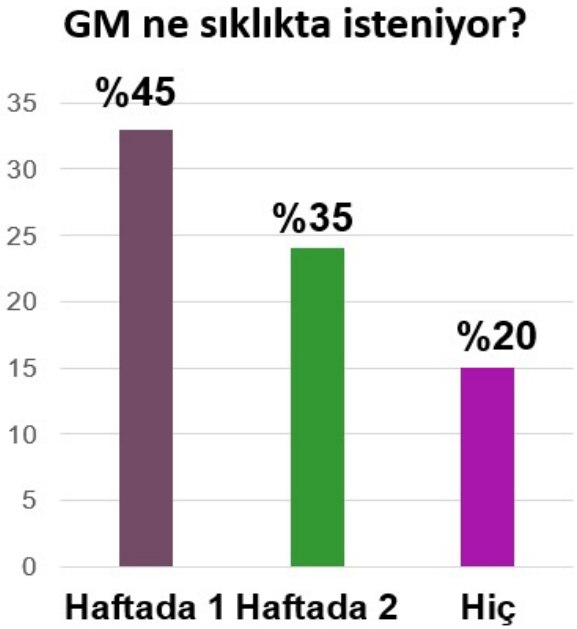
IFI Yönetiminde öneriler;

- Antifungal **profilaksiyi sınırlayın**
- **Hedefe yönelik** tedavi için **yeni teşhis teknikleri** uygulayın
- **Biyobelirteçler** uygulayın (galaktomannan, CAGTA, Beta-d-glukan, T2MR)
- Kritik hastalarda "**erken" antifungal tedavi**
- Yeterli kaynak kontrolünü sağlayın
- **Yeterli doz**: **Azol** alanlarda **TDM**
- **De-eskalasyon**
- **Tedavi süresinin** yönetimi

İFİ anketi







İnvazif Fungal İnfeksiyon Yönetimi

Aktivite tipi	Maya	Küf
Amfoterisin B	**Fungisidal**	**Fungisidal**
Vorikonazol	Fungistatik	Fungisidal
Kaspofungin	Fungisidal	Fungistatik

Klinik deneyim	Aspergillus'a etkililik	Breakthrough Aspergillozis ve mukormikozis gelişimi
Amfoterisin B	+++	-
Vorikonazol	+++	+
Kaspofungin	++	+

Vallejo C, Barberan J. *Rev Esp Quimioter* 2011; 24(3):117-22.

Azoller

- Geniş etki spektrumu
- Konsantrasyon **bağımsız** aktivite
- Etkinlik için EAA/MİK önemli
- İnvazif aspergilloz tedavisinde **vadi düzeyi** önemlidir
- İlaç seviyesi takibi – "***therapeutic drug monitoring***"-TDM

Ekinokandinler

- ✓ **Hızlı** fungisidal
- ✓ Uzun **postantifungal** etki
- ✓ Konsantrasyona bağlı aktivite
- ✓ Doza bağlı lineer FK etki
- ✓ *C.albicans* direnci %2-3
- ✓ *C.glabrata* %3-13
- ✓ ***C.parapsilosis*???**
- ✓ **Anti-biyofilm** , anti-sitokin ve anti-kemokin aktivitesi

L-AMB

- ✓ **1991**'den bu yana kullanılıyor.
  - ✓ K-AMB - 1959
  - ✓ **Geniş spektrum, etkinlik**
  - ✓ **Tolerabilite**
  - ✓ Kombinasyon tedavilerinin ideal partneri
  - ✓ **TDM gerek yok**
  - ✓ **İlaç etkileşimi sıkıntısı yok**
  - ✓ **Anti-biyofilm** etki
  - ✓ İn-vivo ve in vitro önemli sıklıkta **direnç gelişme riski yok**
  - ✓ **Böbrek** hasarında **doz ayarı** gerekmez.
  - ✓ Pediyatrik (**1 ay-18 yaş**) ve **geriyatrik** hastalarda doz ayarlaması gerektirmez

Aversa F et al. *J Chemotherapy.* 29:3, 131-43

İnvazif Fungal İnfeksiyon Yönetimi

I. 2016 IDSA

II. 2017 ECIL-6

III. ESCMID (Küfler 2018)

IV. Yeni çalışmalar

Clinical Infectious Diseases
IDSA GUIDELINE

IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

https://www.uptodate.com/contents/management-of-candidemia-and-invasive-candidiasis-in-adults?topicRef=2462&source=see_link (Erişim: 6.03.2022)

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

II. Tissot. F, et al. *Haematologica* 2017;102:433-44.

Clinical syndrome	IDSA 2016 [82]
Candidemia, non-neutropenic patient	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): *strongly recommended*; *high-quality evidence* Fluconazole 800 mg (12 mg/kg) then 400 mg/d: *strongly recommended*; *high-quality evidence*[a] Lipid formulation AMB (3–5 mg/kg/d): *strongly recommended*; *high-quality of evidence*[b]
Candidemia, neutropenic patient	Echinocandin (Caspofungin 70/50 mg, Micafungin 100 mg, Anidulafungin 200/100 mg): *strongly recommended*; *moderate-quality evidence* Fluconazole 800 mg (12 mg/kg) then 400 mg/d: *weakly recommended*; *low-quality evidence*
Chronic disseminated candidiasis (hepatosplenic)	Lipid formulation AMB (3–5 mg/kg/d) or an echinocandin for several weeks followed by oral fluconazole 400 mg/d: *strongly recommended*; *low-quality evidence*
Candida endocarditis: native valve	Lipid formulation AMB (3–5 mg/kg/d) ± flucytosine 25 mg/kg 4 times/d or high dose echinocandin (Caspofungin 150 mg/d; Micafungin 150 mg/d; Anidulafungin 200 mg/d): *strongly recommended*; *low-quality evidence*
Candida endocarditis: prosthetic valve	Same anti-fungal regimens: *strongly recommended*; *low-quality evidence* Chronic suppressive anti-fungal therapy with fluconazole (400–800 mg daily): *strongly recommended*; *low-quality evidence*
Candida osteomyelitis	Fluconazole 400 mg/d for 6–12 months or an echinocandin for at least 2 weeks followed by fluconazole 400 mg/d for 6–12 months: *strongly recommended*; *low-quality evidence*
Candida chorioretinitis without vitritis	Fluconazolo 800 mg/d then 400–800 mg/d or voriconazole 400 mg × 2/d then 300 mg × 2/d for 4–6 weeks: *strongly recommended*; *low-quality evidence*
Candida chorioretinitis with vitritis	Same as above plus intravitreal injection (AMB deoxycholate 5–10 μg/0.1 mL sterile water or voriconazole 100 μg/0.1 mL sterile water): *strongly recommended*; *low-quality evidence*
Central nervous system candidiasis	Liposomal AMB 5 mg/kg) ± flucytosine 25 mg/kg 4 times/d followed by fluconazole 400–800 mg/kg/d: *strongly recommended*; *low-quality evidence*

IDSA Management of Candidiasis. *CID.* 2016: 62.

ECIL-6; İnvazif kandidozda antifungal tedavi

Kandida türleri	Genel popülasyon	ÖG/KK	Hematoloji hastaları	ÖG/KK
C. *albicans*	Ekinokandinler	**AI**	Ekinokandinler	AII
	Flukonazol	AI	Flukonazol	CII
	Lipozomal AmB	**AI**	Lipozomal AmB	BII
	AmB lipid kompleksi	AII	AmB lipid kompleksi	BII
C. *glabrata*	Ekinokandinler	**AI**	Ekinokandinler	AII
	Lipozomal AmB	BI	Lipozomal AmB	BII
	AmB lipid kompleksi	BII	AmB lipid kompleksi	BII
C. krusei **Oral devamı** ‘Step down’	Ekinokandinler	AII	Ekinokandinler	AIII
	Lipozomal AmB	**BI**	Lipozomal AmB	BII
	AmB lipid kompleksi	BII	AmB lipid kompleksi	BII
	Vorikonazol	BI	Vorikonazol	CII
C.parapsilosis	Flukonazol	AII	Flukonazol	AIII
	Ekinokandinler	BII	Ekinokandinler	BIII

Tissot F, *et al*. ECIL 6. *Haematologica.* 2017; 102: 433-44.

Treatment of candidemia and invasive candidiasis in adults

Condition or treatment group	Primary
Candidemia	
Nonneutropenic adults	An echinocandin (caspofungin 70 mg IV loading dose, then 50 mg IV daily; micafungin 100 mg IV daily; anidulafungin 200 mg IV loading dose, then 100 mg IV daily) is recommended as initial therapy. An alternative for patients who are not critically ill and who are considered unlikely to have fluconazole-resistant *Candida* spp* is fluconazole 800 mg (12 mg/kg) oral loading dose, then 400 mg (6 mg/kg) orally¶ daily. A lipid formulation of amphotericin B (3 to 5 mg/kg IV daily) is an alternative if there is intolerance, limited availability, or resistance to other antifungal agents.

https://www.uptodate.com/contents/management-of-candidemia-and-invasive-candidiasis-in-adults?topicRef=2462&source=see_link (Erişim: 6.03.2022)

Original Article

Journal of Infection and Chemotherapy 27 (2021) 1471–1476

Efficacy of early administration of liposomal amphotericin B in patients with septic shock: A nationwide observational study

Masato Tashiro [a,b,*], Takahiro Takazono [a,c], Yuki Ota [d], Tomotaro Wakamura [e], Akinori Takahashi [f], Kumiko Sato [f], Taiga Miyazaki [a,c], Yoko Obata [d], Tomoya Nishino [d], Koichi Izumikawa [a,b]

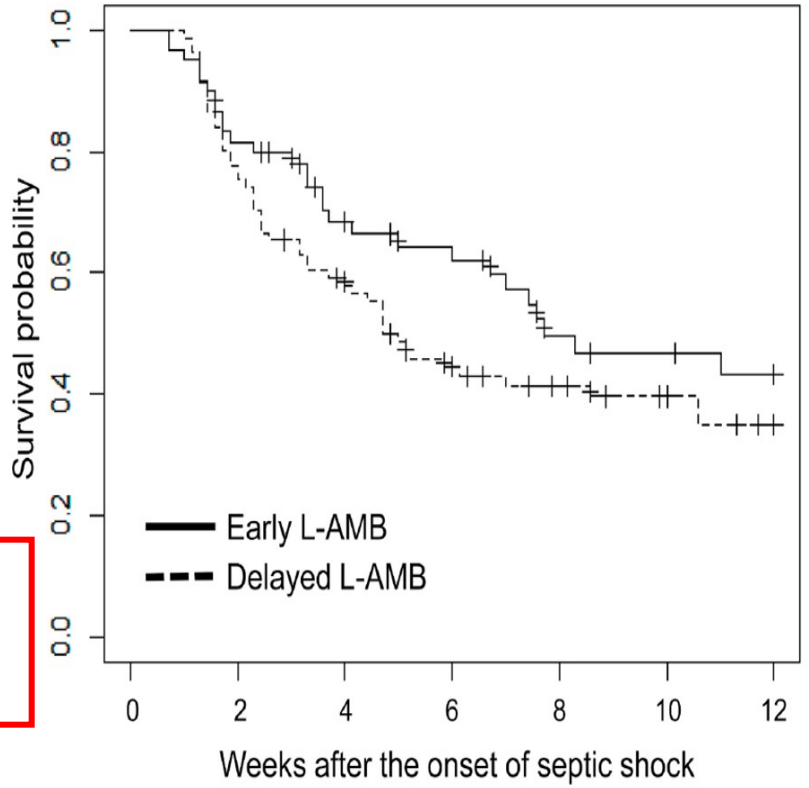
Çok Merkezli, retrospektif

Septik şok: 141

- 60 hasta **erken L-AMB** tedavisi (early L-AMB)
- 81 hasta **gecikmiş L-AMB** tedavisi (septik şok görülmesinden sonraki gün) (delayed L-AMB)

•Erken L-AMB grubunda **septik şok kesilme süresi daha kısa** bulunmuştur

Septik şok başlangıcında **erken L-AMB uygulaması, şokun erken kesilmesiyle ilişkili olabilir.**



Assessing the Bioactive Profile of Antifungal-Loaded Calcium Sulfate against Fungal Biofilms

Mark C. Butcher,[a] Jason L. Brown,[a] Donald Hansom,[a,b] Rebecca Wilson-van Os,[c] Craig Delury,[c] Phillip A. Laycock,[c] Gordon Ramage[a]

[a]Oral Sciences Research Group, Glasgow Dental School, School of Medicine, Dentistry and Nu
Glasgow, Glasgow, United Kingdom
[b]Forth Valley Royal Hospital, Larbert, United Kingdom
[c]Biocomposites, Ltd., Keele, Staffordshire, United Kingdom

June 2021 Volume

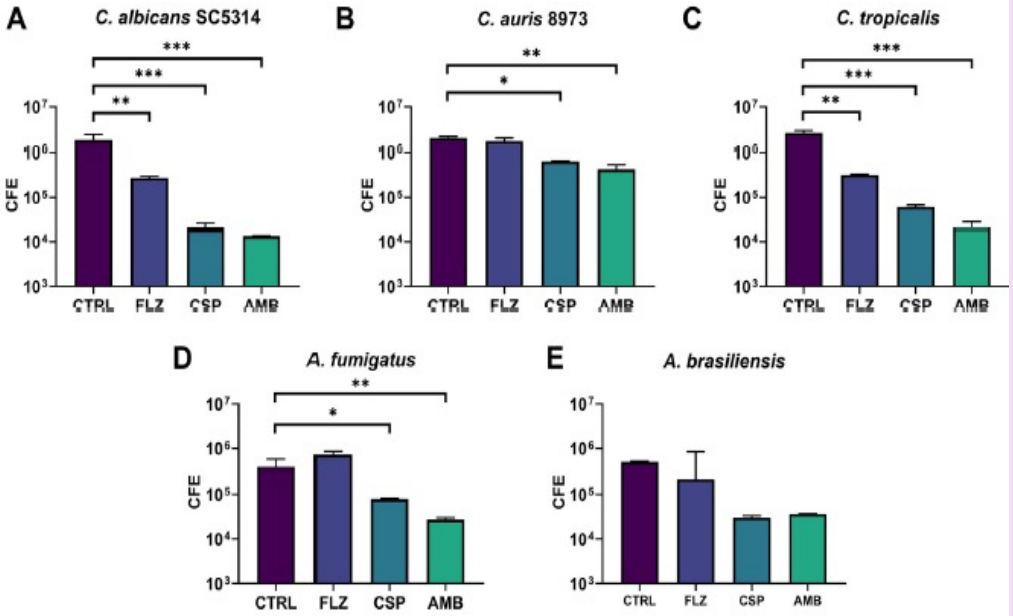


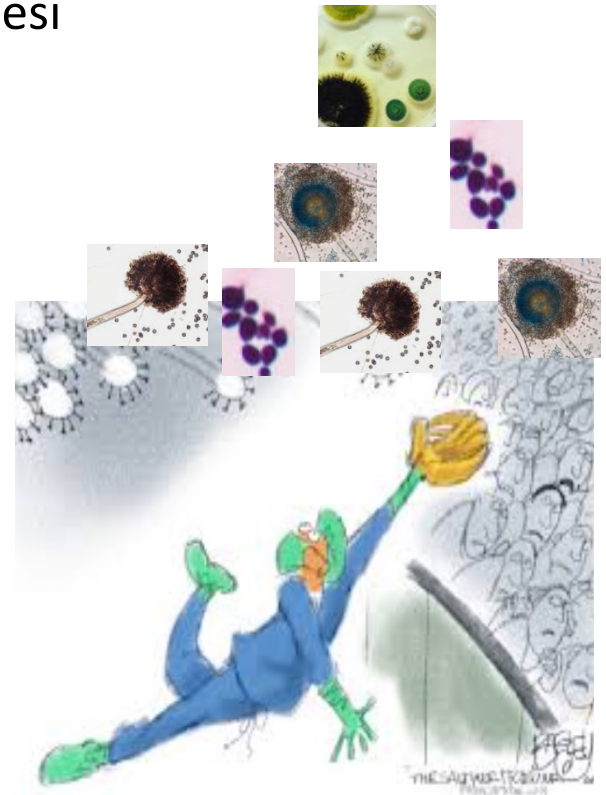
FIG 4 Total qPCR of fungal biofilm treated with antifungal CS after 48 h. Bars represent log CFE of 5 tested fungal isolates (A to E). Results indicate a variable but statistically significant reduction in total CFE for all but one isolate when exposed to CSP- and AMB-loaded beads, while FLZ-loaded beads only proved effective ($P < 0.005$) versus *C. albicans* SC5314 (A), *C. auris* 8973 (B), and *C. tropicalis* (C). In *A. brasiliensis* (E), no significant change ($P < 0.05$) was determined.

- ✓ ***C. albicans***
  - ✓ **140-fold reduction with AMB-loaded** beads (P<0.0005)
  - ✓ 95-fold reduction with CSP-loaded beads (P < 0.0005),
  - ✓ 7-fold reduction with FLZ-loaded beads (P < 0.005).
- ✓ ***C. auris***
  - ✓ **4.5-fold reduction with AMB-loaded** beads (P < 0.001),
  - ✓ 3-fold drop with CSP-loaded beads (P < 0.005)
  - ✓ no significant reduction with FLZ-loaded beads.
- ✓ ***C. tropicalis***
  - ✓ **120-fold reduction with AMB-loaded** beads
  - ✓ 40-fold reduction with CSP-loaded beads
  - ✓ 8-fold reduction with FLZ-loaded beads

Butcher MC et al. Antimicrob Agents Chemother. 2021;65(6):e02551-20

Sonuç olarak

- İFİ'ler immünokompromize konakta /YBÜ'de **hayatı tehdit** eder
- Ampirik & tanı güdümlü yönetim gerektirir
- **Lokal veriler**, **direnç sonuçlarının** güncel takip edilmesi gereklidir
- Antifungal **tedavinin erken başlanması** önemlidir
- Tedavide **ilaç etkileşimleri** akılda tutulmalıdır
- Serum **ilaç düzeyi takibi** özellikle **YBÜ** hastalarında gereklidir
- Antifungal yönetim **ekip işidir**.



Doğayla barışık birlikte sağlıkla yaşamak mümkün