YOĞUN BAKIMLARDA İNVAZİV KANDİDİYAZ YÖNETİMİ

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International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

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Context Infection is a major cause of morbidity and mortality in intensive care units (ICUs) worldwide. However, relatively little information is available about the global epidemiology of such infections.

Objective To provide an up-to-date, international picture of the extent and patterns of infection in ICUs.

Design, Setting, and Patients The Extended Prevalence of Infection in Intensive Care (EPIC II) study, a 1-day, prospective, point prevalence study with follow-up conducted on May 8, 2007. Demographic, physiological, bacteriological, therapeutic, and outcome data were collected for 14 414 patients in 1265 participating ICUs from 75 countries on the study day. Analyses focused on the data from the 13 796 adult (>18 years) patients.

Results On the day of the study, 7087 of 13 796 patients (51%) were considered infected; 9084 (71%) were receiving antibiotics. The infection was of respiratory origin in 4503 (64%), and microbiological culture results were positive in 4947 (70%) of the infected patients; 62% of the positive isolates were gram-negative organisms, 47% were gram-positive, and 19% were fungi. Patients who had longer ICU stays prior to the study day had higher rates of infection, especially infections due to resistant staphylococci, *Acinetobacter*, *Pseudomonas* species, and *Candida* species. The ICU mortality rate of infected patients was more than twice that of noninfected patients (25% [1688/6659] vs 11% [682/6352], respectively; $P<.001$), as was the hospital mortality rate (33% [2201/6659] vs 15% [942/6352], respectively; $P<.001$) (adjusted odds ratio for risk of hospital mortality, 1.51; 95% confidence interval, 1.36-1.68; $P<.001$).

Conclusions Infections are common in patients in contemporary ICUs, and risk of infection increases with duration of ICU stay. In this large cohort, infection was independently associated with an increased risk of hospital death.

JAMA. 2009;302(21):2323-2329 www.jama.com

Vincent JL, JAMA, 2009

INFECTION IS A COMMON PROBLEM FOR patients in intensive care units (ICUs) and is associated with considerable morbidity, mortality, and costs.[1-4] Infection and related sepsis are the leading cause of death in noncardiac ICUs, with mortality rates that reach 60% and account for approximately 40% of total ICU expenditures.[1,5] Importantly, the incidence of sepsis is increas-

Table 2. Infection Rates and Types of Organisms in Culture-Positive Infected Patients According to Geographical Region

	No. (%)[a]							
	All	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
No. (%)	7087 (51.4)	3683 (49)	426 (56.4)	1290 (60.3)	607 (48.4)	285 (48.2)	89 (46.1)	707 (52.6)
Site of infection								
Respiratory tract	4503 (63.5)	2332 (63.3)	305 (71.6)[b]	851 (66)	345 (56.8)[b]	165 (57.9)	41 (46.1)[b]	464 (65.6)
Abdominal	1392 (19.6)	778 (21.1)	93 (21.8)	228 (17.7)[b]	101 (16.6)	50 (17.5)	16 (18)	126 (17.8)
Bloodstream	1071 (15.1)	546 (14.8)	53 (12.4)	139 (10.8)[b]	157 (25.9)[b]	49 (17.2)	16 (18)	111 (15.7)
Renal/urinary tract	1011 (14.3)	411 (11.2)	84 (19.7)[b]	222 (17.2)[b]	135 (22.2)[b]	32 (11.6)	15 (16.9)	111 (15.7)[b]
Skin	467 (6.6)							
Catheter-related	332 (4.7)							
CNS	208 (2.9)							
Others	540 (7.6)							
Microorganisms								
Positive isolates	4947 (69.8)	2						
Gram-positive	2315 (46.8)	1						
Staphylococcus aureus	1012 (20.5)							
MRSA	507 (10.2)							
S epidermidis	535 (10.8)							
Streptococcus pneumoniae	203 (4.1)							
VSE	352 (7.1)							
VRE	186 (3.8)							
Other	319 (6.4)							
Gram-negative	3077 (62.2)	1						
Escherichia coli	792 (16.0)							
Enterobacter	345 (7.0)							
Klebsiella species	627 (12.7)							
Pseudomonas species	984 (19.9)							
Acinetobacter species	435 (8.8)							
Other	840 (17.0)							
ESBL-producing	93 (1.9)							
Anaerobes	222 (4.5)							
Other bacteria	76 (1.5)							
Fungi								
Candida	843 (17)	495 (18.5)	66 (18.5)	92 (12.8)[b]	83 (18.2)	26 (12.7)	6 (11.1)	75 (15.7)
Aspergillus	70 (1.4)	44 (1.6)	1 (0.3)	5 (0.7)	12 (2.6)	3 (1.5)	0	5 (1)
Other	50 (1)	22 (0.8)	5 (1.4)	7 (1)	10 (2.2)	2 (1)	0	4 (0.8)
Parasites	34 (0.7)	18 (0.7)	2 (0.6)	6 (0.8)	3 (0.7)	2 (1)	0	3 (0.6)
Other organisms	192 (3.9)	122 (4.6)	9 (2.5)	15 (2.1)[b]	22 (4.8)	8 (3.9)	2 (3.7)	14 (2.9)

Abbreviations: CNS, central nervous system; ESBL, extended-spectrum β-lactamases; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; VSE, vancomycin-sensitive *Enterococcus*.

[a] Percentages do not necessarily equal 100, because patients may have had more than 1 type of infection or microorganism.

[b] Significant at 5% (with Bonferroni correction) vs Western Europe.

Mikroorganizma sıralaması

Staphylococcus aureus %20.5

Pseudomonas spp %19.9

***Candida spp* %17**

E coli %16

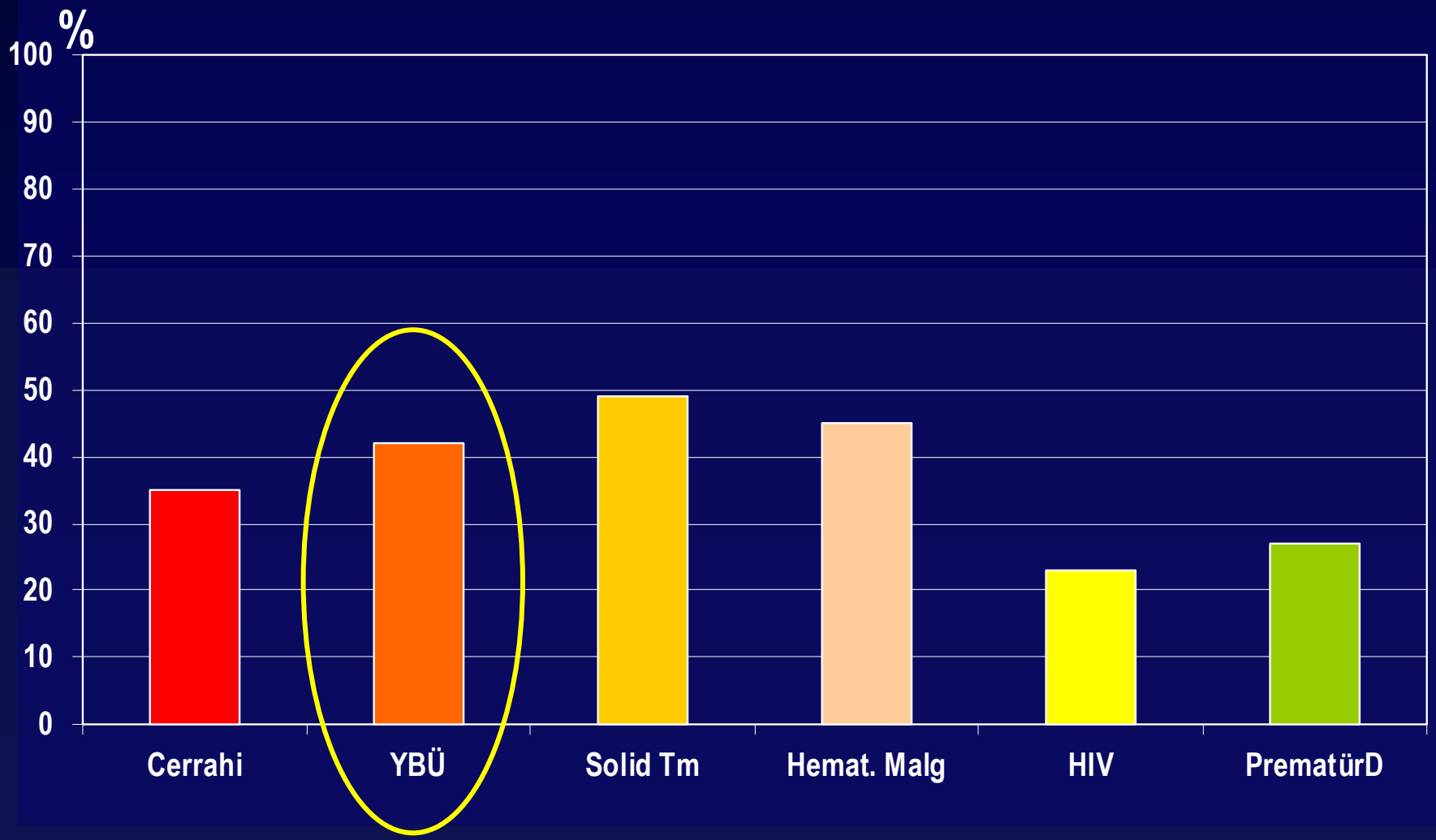
Klebsiella spp %13.7

Acinetobacter spp % 8.8

Enfekte hastalarda mortalite %25

Vincent JL, JAMA, 2009

İnvaziv *Candida* infeksiyonunda mortalite



Tortorano et al, EJCMID 2004; 23: 317

Candida türlerinin dağılımı

2008-2009, SENTRY

Table 2

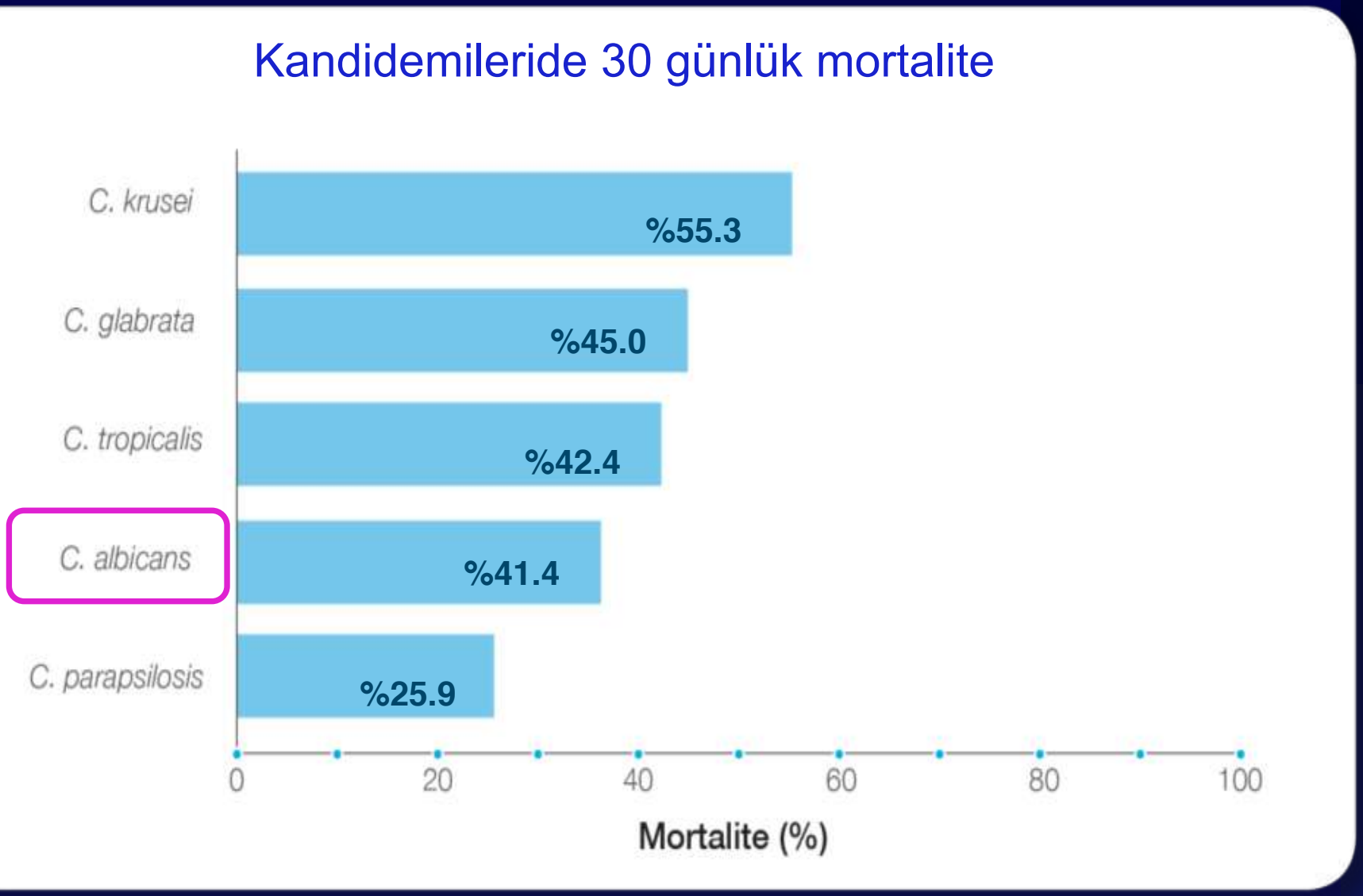
Species distribution of *Candida* bloodstream infection isolates from Intensive Care Unit (ICU) and non-ICU locations.

Species	*n* (%) of each species according to origin	
	ICU (*N* = 779)	Non-ICU (*N* = 973)
C. albicans	393 (50.4)	461 (47.4)
C. glabrata	136 (17.5)	176 (18.1)
C. parapsilosis	118 (15.1)	184 (18.9)
C. tropicalis	82 (10.5)	93 (9.6)
C. krusei	16 (2.1)	20 (2.1)
Miscellaneous[a]	34 (4.4)	39 (4.0)

[a] Miscellaneous species including *C. lusitaniae* (31 isolates), *C. dubliniensis* (16 isolates), *C. guilliermondii* (8 isolates), *C. kefyr* (6 isolates), *C. famata* and *C. lipolytica* (3 isolates each) and *C. rugosa*, *C. sake* and *C. pelliculosa* (2 isolates each).

Pfaller MA, IJAA, 2011

Kandidemide etken ilişkili mortalite



Tortorano A, et al. Eur J Clin Microbiol Infect Dis. 2004;23(4):317-22

İnvazif *Candida* enfeksiyonlarında dağılım / direnç / mortalite

Table 1. Candidaemia epidemiology from population-based or multicentre studies

Country	Years covered	Number of candidaemia episodes	Annual incidence rate	Proportion *C. albicans*/ non-*albicans*	Rate of azole resistance	30 day mortality rate	Reference
USA	2008–11	2675	13.3–26.2/100 000 population	37/63	7%	28%–29%	7
USA	2013	515	9.5–14.4/100 000 population	35/65	5%–7%	NA	8
Canada	2003–05	453	3.0/100000 population	62/38	4%	NA	143
Norway	2004–12	1677	3.9/100000 population	68/32	7%	NA	11
Finland	2004–07	603	2.9/100000 population	67/33	NA	35%	144
Iceland	2000–11	208	5.7/100000 population	56/44	3%	30%	145
Denmark	2004–09	2649	8.6/100000 population	58/42	NA	NA	13
France	2001–10	15 570	3.6/100000 population	NA	NA	NA	146
Spain	2010–11	773	8.1/100000 population	45/55	21%	31%	14
Belgium	2013–14	338	0.4/1000 admissions	50/50	8%	NA	28
Scotland	2007	242	4.8/100000 population	50/50	2%	NA	29
Australia	2001–04	1095	1.8/100000 population	47/53	NA	28%	147
Australia	2014–15	527	2.4/100000 population	44/56	6%	NA	10
Brazil	2007–10	137	NA	34/66	9%	72%	30
Peru	2013–15	157	2.0/1000 admissions	28/72	3%	40%	148
Latin America	2008–10	672	0.3–2.0/1000 admissions	38/62	3%	41%	31
South Africa	2009–10	2172	NA	46/54	18%	NA	33
Asia-Pacific	2010–11	1601	0.3–2.9/1000 discharges	41/59	NA	NA	20
India	2011–12	1400	6.5/1000 admissions[a]	21/79	12%	45%	35

Lamoth F, JAC, 2018

RESEARCH Open Access

Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project

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Abstract

Background: The objective of this study was to assess the cumulative incidence of invasive candidiasis (IC) in intensive care units (ICUs) in Europe.

Methods: A multinational, multicenter, retrospective study was conducted in 23 ICUs in 9 European countries, repre NDICU).

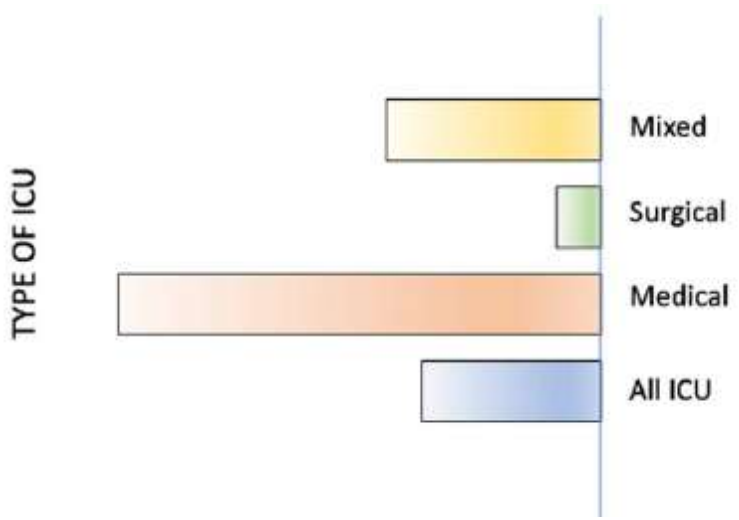
30 günlük mortalite oranı %42

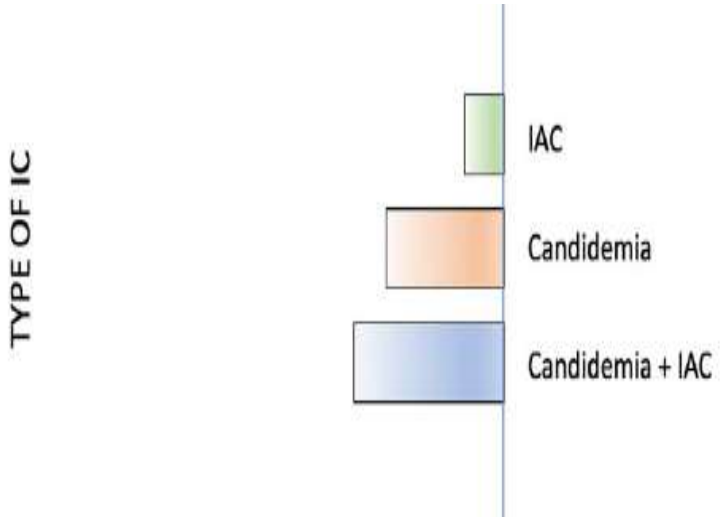
Resu ence of 7.07 episodes per 1000 ICU admissions, with important between-center variability. Separated, non-mutually exclusive cumulative incidences of candidemia and IAC were 5.52 and 1.84 episodes per 1000 ICU admissions, respectively. Crude 30-day mortality was 42%. Age (odds ratio [OR] 1.04 per year, 95% CI 1.02–1.06, $p < 0.001$), severe hepatic failure (OR 3.25, 95% 1.31–8.08, p 0.011), SOFA score at the onset of IC (OR 1.11 per point, 95% CI 1.04–1.17, p 0.001), and septic shock (OR 2.12, 95% CI 1.24–3.63, p 0.006) were associated with increased 30-day mortality in a secondary, exploratory analysis.

Conclusions: The cumulative incidence of IC in 23 European ICUs was 7.07 episodes per 1000 ICU admissions. Future in-depth analyses will allow explaining part of the observed between-center variability, with the ultimate aim of helping to improve local infection control and antifungal stewardship projects and interventions.

Keywords: ICU, Candidemia, Candidiasis, *Candida*, Abdominal candidiasis, Incidence

Center-level variables*	Number of IC episodes	Number of ICU admissions	Cumulative incidence (IC episodes/1000 ICU admi
Year of study			
2015	271	40,642	6.67
2016	299	40,003	7.47
Type of ICU			
Medical ($n = 5$)	149	7828	19.03
Surgical ($n = 3$)	51	29,087	1.75
Mixed (medical plus surgical, $n = 15$)	370	43,730	8.46





Bassetti M, Crit Care 2019

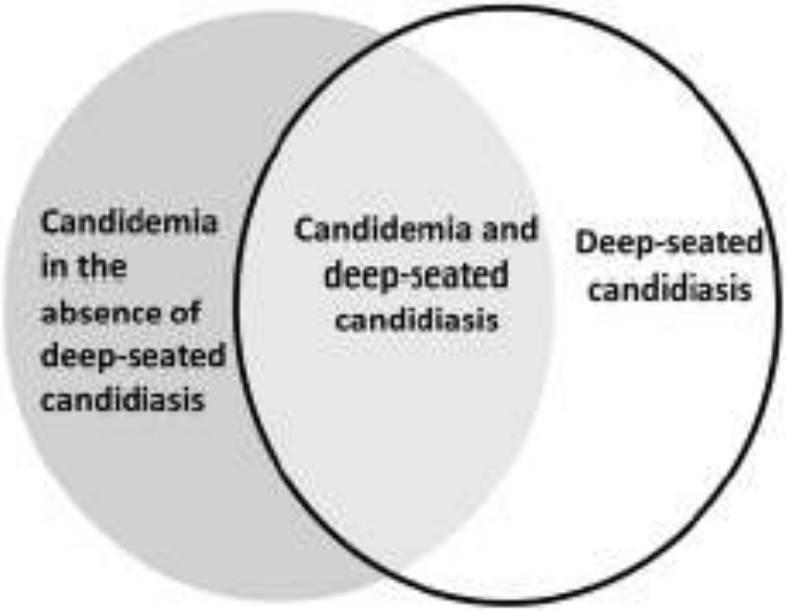
İnvaziv kandidiaz tipleri

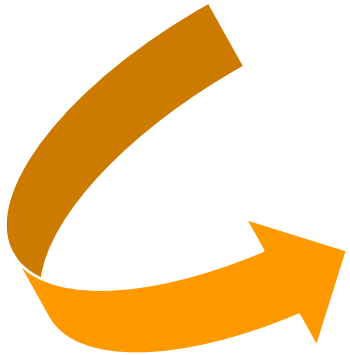
- %40 kandidemi (derin doku tutulumu yok)
- %28 kandidemi (derin doku tutulumu ile birlikte)
- %32 kan kültürü (-) *Candida* derin doku enfeksiyonu

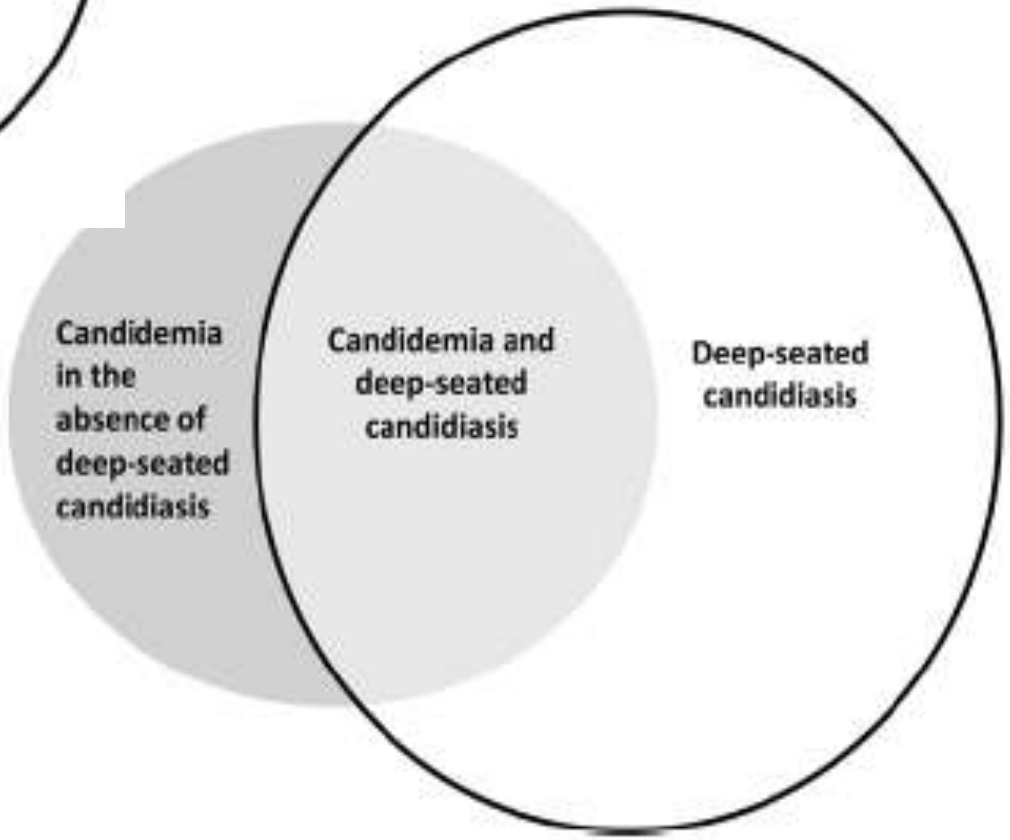
- Kan kültürü ile kabaca %70 'I yakalanabiliyor

Leroy at al, Critical care 2009, Clancy et al, Clin infect dis 2013

Diagnostik yöntemler geliştirildiğinde kan kültrü negatif derin doku enfeksiyonları daha iyi yakalanacaktır







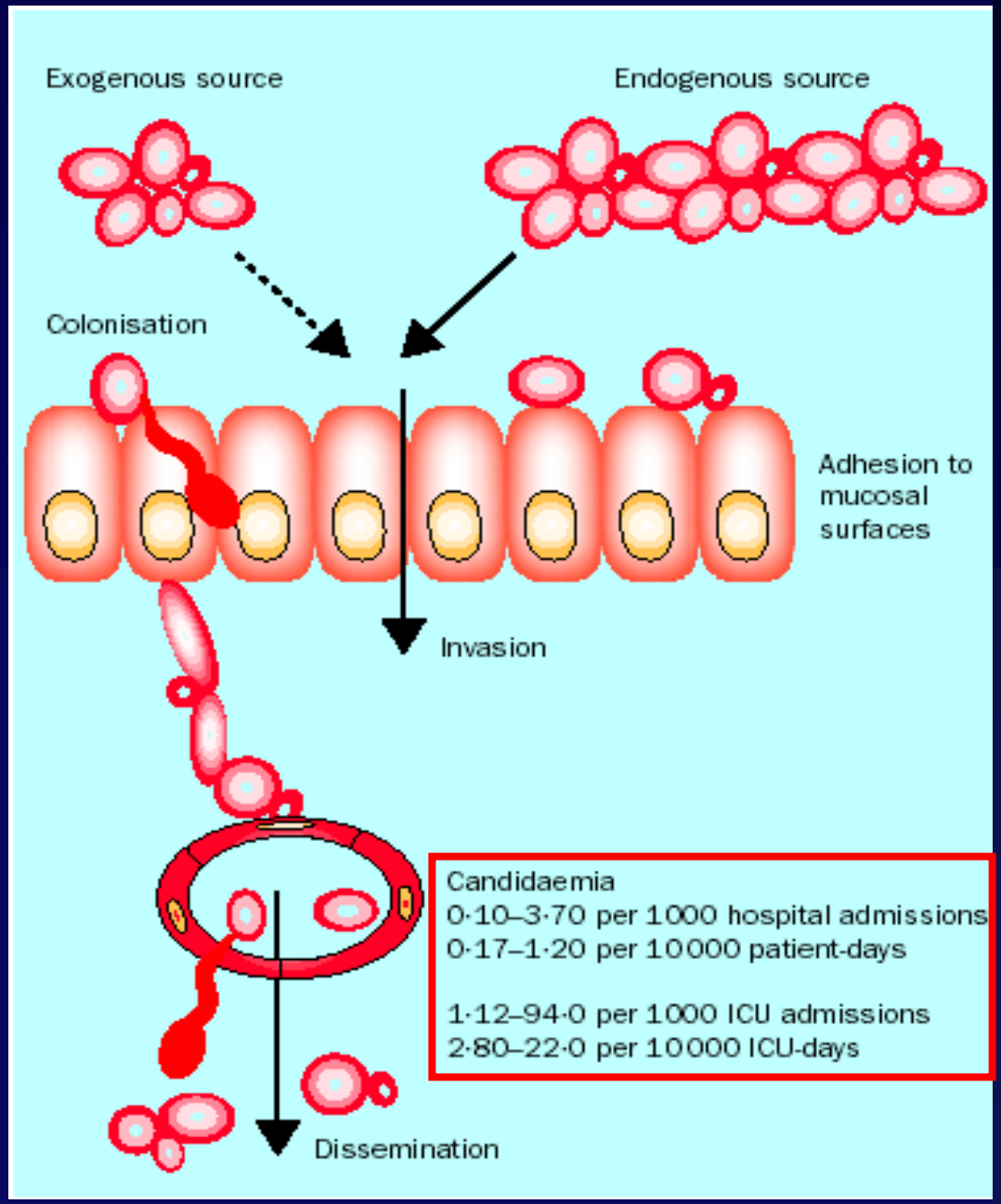
Leroy at al, Critical care 2009, Clancy et al, Clin infect dis 2013

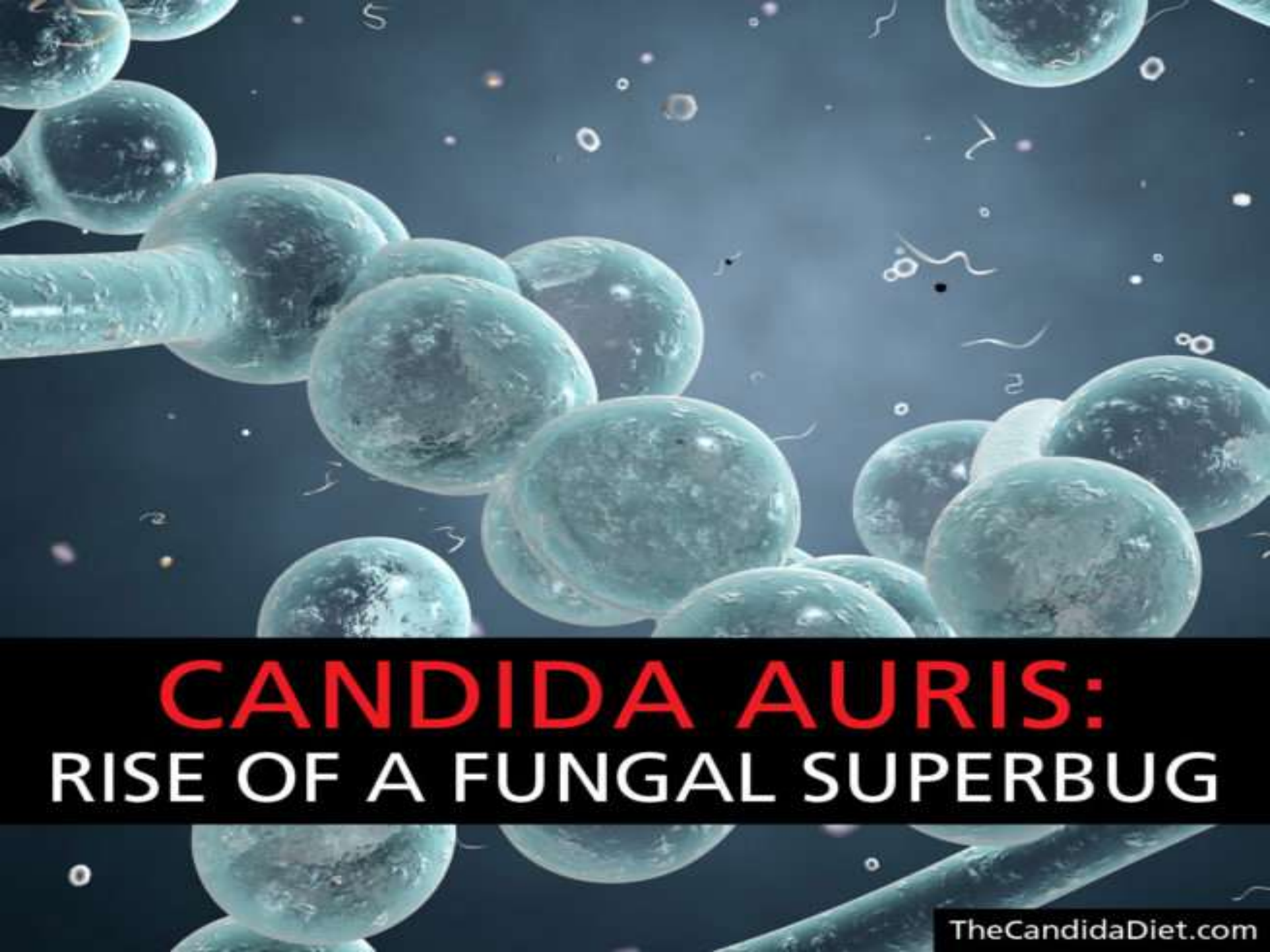
Endojen (en sık)

- GİS
- Cilt
- Mukoza

Eksojen (nozokomiyal)

- Sağlık çalışanı
- Kolonize aletler




CANDIDA AURIS:
RISE OF A FUNGAL SUPERBUG
TheCandidaDiet.com

CDC 30 Eylül 2019, Dünyada C auris Epidemiyolojisi

Nozokomiyal bulaş gösteren, azol direnç oranı yüksek bir tür

Azol kullanım öyküsü varsa direnç riski yüksek

Table 4 In vitro azole resistance in the presence/absence of exposure to azole prophylaxis

Azole prophylaxis exposure	Drugs	No. of isolates	No. (%) of isolates resistant[c]
Absence[a]	Fluconazole	72	2 (2.8)
	Voriconazole	72	2 (2.8)
	Posaconazole	72	0
Presence[b]	Fluconazole	17	8 (47.0)
	Voriconazole	17	10 (58.8)
	Posaconazole	17	6 (35.3)

Montagna MT, Infection, 2013

MAJOR ARTICLE

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

Kevin W. Garey,[1] Milind Rege,[1] Manjunath P. Pai,[2] Dana E. Mingo,[3] Katie J. Suda,[4] Robin S. Turpin,[5] and David T. Bearden[6]

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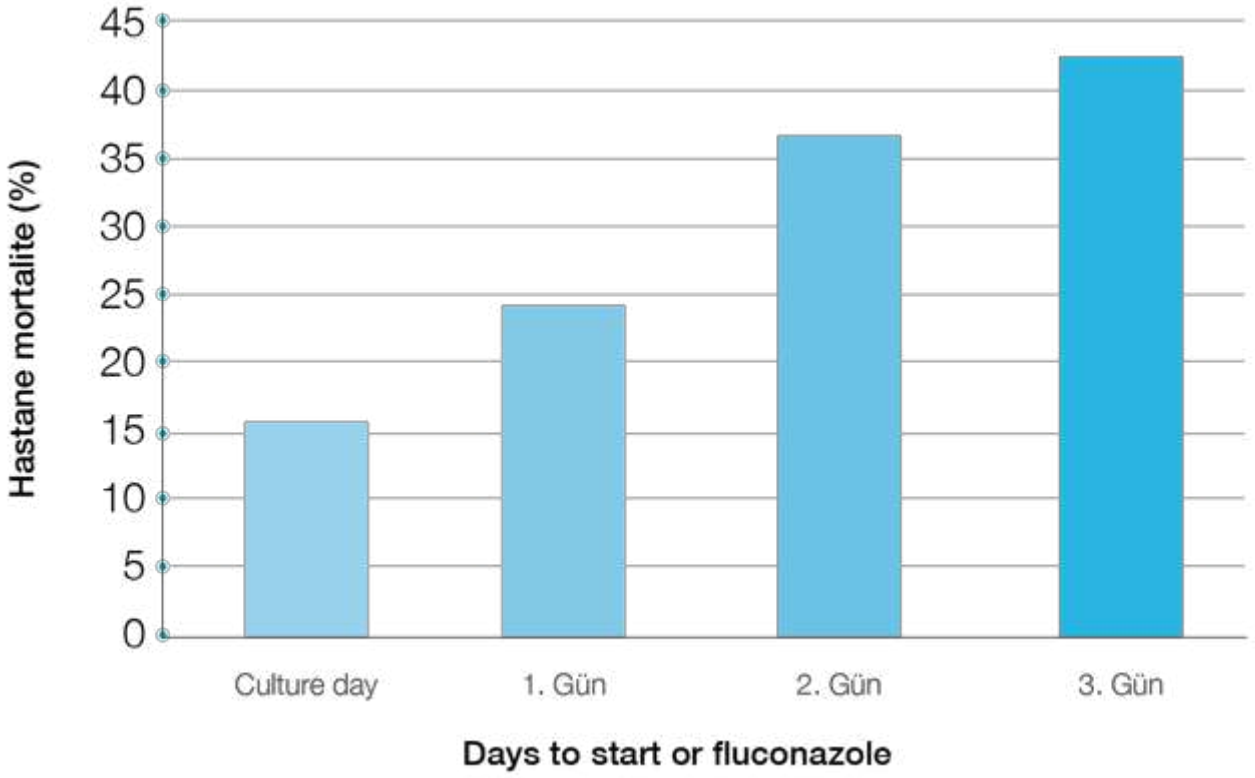
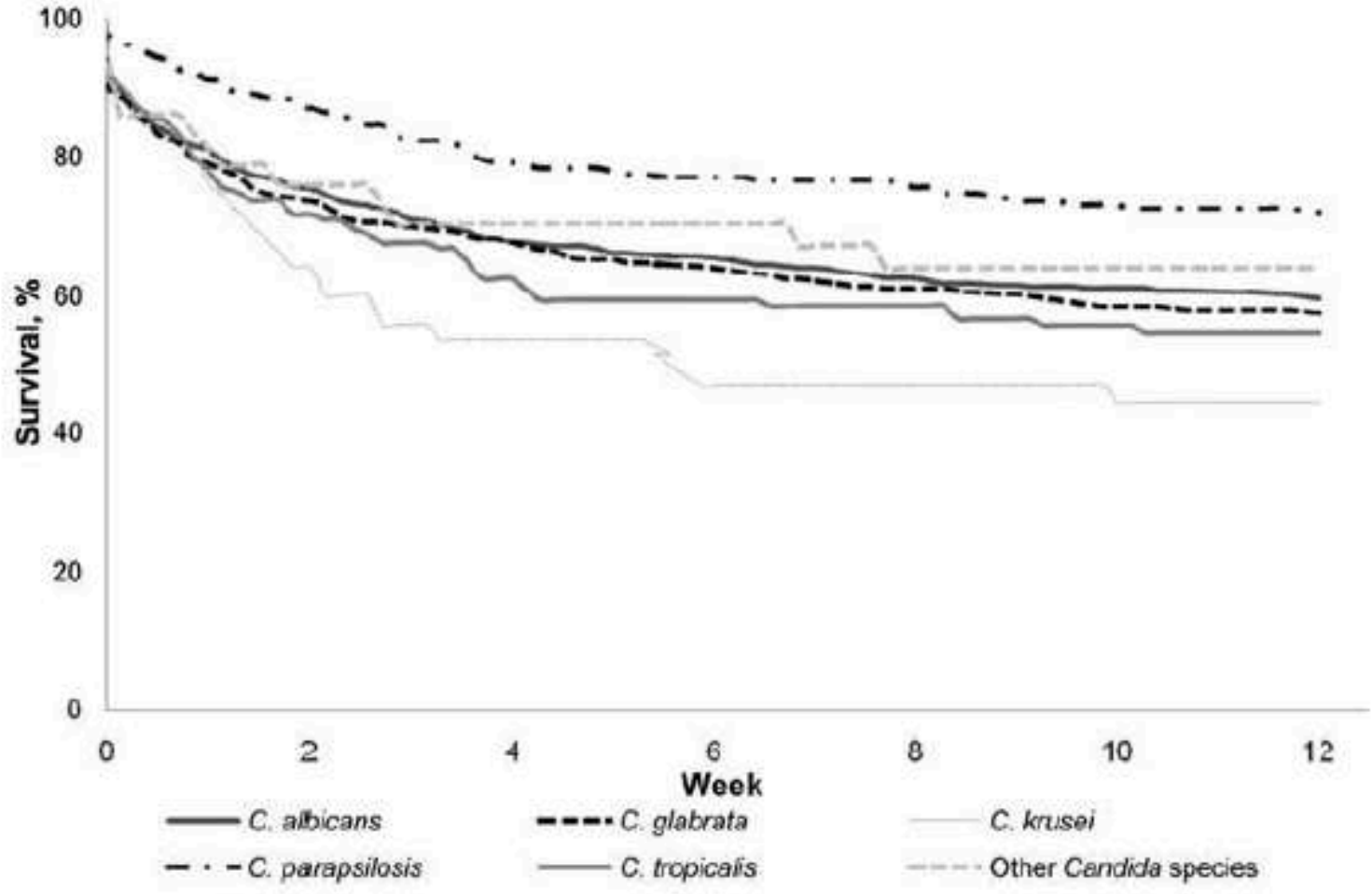


Garey KW, Clin Infect Dis 2006;43:25

Etkenler ve Mortalite
Prospective Antifungal Therapy Alliance Registry



Horn D, CID, 2009

İnvazif Kandidiyaz Kesin Tanısı

- **Kan kültürü pozitifliği**
  - **Kandidemide ortalama %50** (%21 – 71) pozitif
  - Sonuç alınması median 2-3 gün
- **Steril vücut sıvısı ya da dokuda üretilmesi**
- **Histolojik tanı**

İnvaziv Fungal Enfeksiyonların Tanısı

	Candida	*Aspergillus*	Mucorales	*Fusarium*	*Cryptococc*
Kültür	✓	✓	✓	✓	✓
Histopatoloji	✓	✓	✓	✓	✓
Galaktomannan		✓		✓	
Beta glukan	✓	✓		✓	
Lateral Flow test	✓	✓			✓
T2 Manyetik Rezonans	✓				
PCR	✓	✓	✓	✓	✓
Mannan Anti-Mannan	✓				

CAGTA +

Odabaşı Z, Türkiye Klin Der, 2019

Table 2. Performance of Blood Cultures in Autopsy Studies of Invasive Candidiasis

Reference	Year	No. of Patients	Underlying Disease	Sensitivity
Louria (from [13])	1962	19	Hematologic malignancies, solid tumors, medical and surgical conditions	42%
Bodey (from [13])	1966	61	Acute leukemia	25%
Taschdjian (from [13])	1969	17	Malignancies and other medical conditions	47%
Hart (from [13])	1969	16	Hematologic malignancies, solid tumors, transplant, medical and surgical conditions	44%
Bernhardt (from [13])	1972	14	Transplant and surgical conditions	36%
Gaines (from [13])	1973	26	Hematologic malignancies, solid tumors, medical and surgical conditions	54%
Myerowitz (from [13])	1977	39	Hematologic malignancies, solid tumors, medical and surgical conditions	44%
Ness [9]	1989	7	Hematologic malignancies and bone marrow transplant recipients	71%
Singer [37]	1977	16	Hematologic malignancies	31%
Berenguer [13]	1993	37	Mostly hematologic malignancies and solid tumors	43%
Van Burik [38]	1998	62	Bone marrow transplant recipients	52%
Kami [39]	2002	91	Hematologic malignancies	21%
Thorn [40]	2010	10	Hematologic malignancies, gastrointestinal disease, transplant, prematurity	50%

Clancy JC, CID 2013

Table 1
Contemporary diagnostic methods in medical mycology

Diagnostic Method	Sensitivity and Specificity (%)	Turn-Around Time	Comments
Candida			
Blood culture	50 and 100[15]	2–3 d	Sensitivity depends on the source of infection
β-D-Glucan	75 and 80[18]	2–4 h	Risk of false-positives in ICU patients is high. Specificity is improved with consecutive repeated tests, and is affected by presence of other fungal infections
Mannan/ antimannan	83 and 75–86[80,81]	2–4 h	Not available in United States
Polymerase chain reaction	80–95 and 70–90[23,82]	4–5 h	Lack of consensus regarding standardization Sensitivity and specificity vary among the available commercial tests
T2Candida Panel	91 and 99[83]	4 h	New technology. Limited availability because of cost

T2Candida Panel

Sensitivity: 91%[3]

Specificity: 99%[3]

Candida albicans

Candida tropicalis

Candida krusei

Candida glabrata

Candida parapsilosis

MAJOR ARTICLE

T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial

Eleftherios Mylonakis,[1] Cornelius J. Clancy,[2] Luis Ostrosky-Zeichner,[3] Kevin W. Garey,[4] George J. Alangaden,[5] Jose A. Vazquez,[6] Jeffrey S. Groeger,[7] Marc A. Judson,[8] Yuka-Marie Vinagre,[9] Stephen O. Heard,[10] Fainareti N. Zervou,[1] Ioannis M. Zacharioudakis,[1] Dimitrios P. Kontoyiannis,[11] and Peter G. Pappas[12]

[1]Infectious Diseases Division, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence; [2]Veterans Affairs Pittsburgh Healthcare System, Division of Infectious Diseases, University of Pittsburgh, Pennsylvania; [3]Division of Infectious Diseases, University of Texas Medical School at Houston and Memorial Hermann Texas Medical Center; [4]University of Houston College of Pharmacy, Texas; [5]Division of Infectious Diseases,

Table 2. Overall Sensitivity and Specificity of the T2 Magnetic Resonance Method

Sensitivity	No.	%	95% CI
Overall per patient[a]	233/256	91.0	86.8–94.2
Overall per assay[a]	234/257	91.1	86.9–94.2
Per *Candida* species[a]			
C. albicans/tropicalis	96/104	92.3	85.4–96.6
C. parapsilosis	49/52	94.2	84.1–98.8
C. krusei/glabrata	89/101	88.1	80.2–93.7

Conclusions. T2MR is the first fully automated technology that directly analyzes whole blood specimens to identify species without the need for prior isolation of *Candida* species, and represents a breakthrough shift into a new era of molecular diagnostics.

Kolonizasyon indeksi

- Kandidiyaz riski bulunan cerrahi YBÜ hastaları
- **Nasıl hesaplanır?**
  - Oral, perianal, yara yeri ,DTA vb bir çok bölgeden örnekleme
  - Kandida üremesi / kültür gönderilen bölge sayısı
- Pitet çalışmasında: ortalama kolonizasyon indeksi:
  - Kolonize hastalarda 0.47
  - Enfekte hastalarda 0.7 ($p < 0.01$)
- **≥ 0.5 indeks ile 6 gün erken tedavi başlanabilir**

Pitet et al, 1994, Ann Surg

Kandida Skoru (Leon skoru)

- >7 gün yatan 1699 ICU vakasında prospektif kohort
- Skorlamada bakılan kriterler:
  - Cerrahi (1 puan)
  - Multifokal kolonizasyon (1 puan)
  - TPN (1 puan)
  - Ağır sepsis (2 puan)
- ≥ 3 skor ile %81 duyarlılık, %74 özgüllük
- PPV %16
- NPV %98

Leon C, Crit Care Med, 2006

Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, *Candida* score, and colonization index

Brunella Posteraro[1], Gennaro De Pascale[2], Mario Tumbarello[3*], Riccardo Torelli[1], Mariano Alberto Pennisi[2], Giuseppe Bello[2], Riccardo Maviglia[2], Giovanni Fadda[1], Maurizio Sanguinetti[1] and Massimo Antonelli[2]

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
BG cut-off value, 80 pg/mL	92.9 (66.1 to 99.8)	93.7 (85.8 to 97.9)	72.2 (46.5 to 90.3)	98.7 (92.8 to 99.9)
CS ≥3	85.7 (57.2 to 98.2)	88.6 (79.5 to 94.7)	57.1 (34.0 to 78.2)	97.2 (90.3 to 99.7)
Colonization index ≥0.5	64.3 (35.1 to 87.2)	69.6 (58.2 to 79.5)	27.3 (13.3 to 45.5)	91.7 (81.6 to 97.2)

Posteraro B, Crit Care, 2011

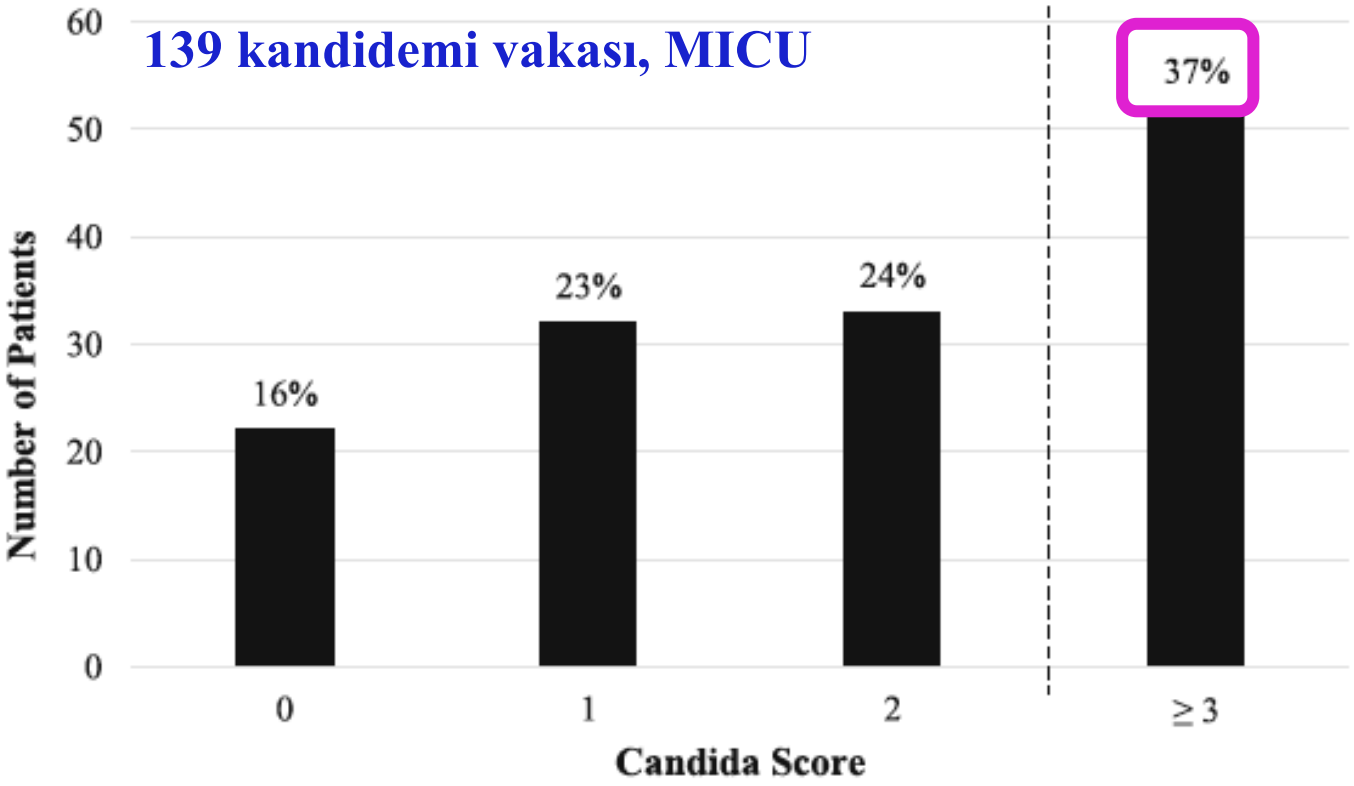
Laine *et al. Critical Care* (2019) 23:242
https://doi.org/10.1186/s13054-019-2525-3

Critical Care

LETTER Open Access

Need for expanded Candida Score for empiric antifungal use in medically critically ill patients?

Melanie E. Laine[1,2*], Alexander H. Flannery[1,2], Breanna Moody[3] and Melissa L. Thompson Bastin[1,2]



Cortegiani et al. Critical Care (2019) 23:190
https://doi.org/10.1186/s13054-019-2481-y

Critical Care

RESEARCH Open Access

Procalcitonin levels in candidemia versus bacteremia: a systematic review

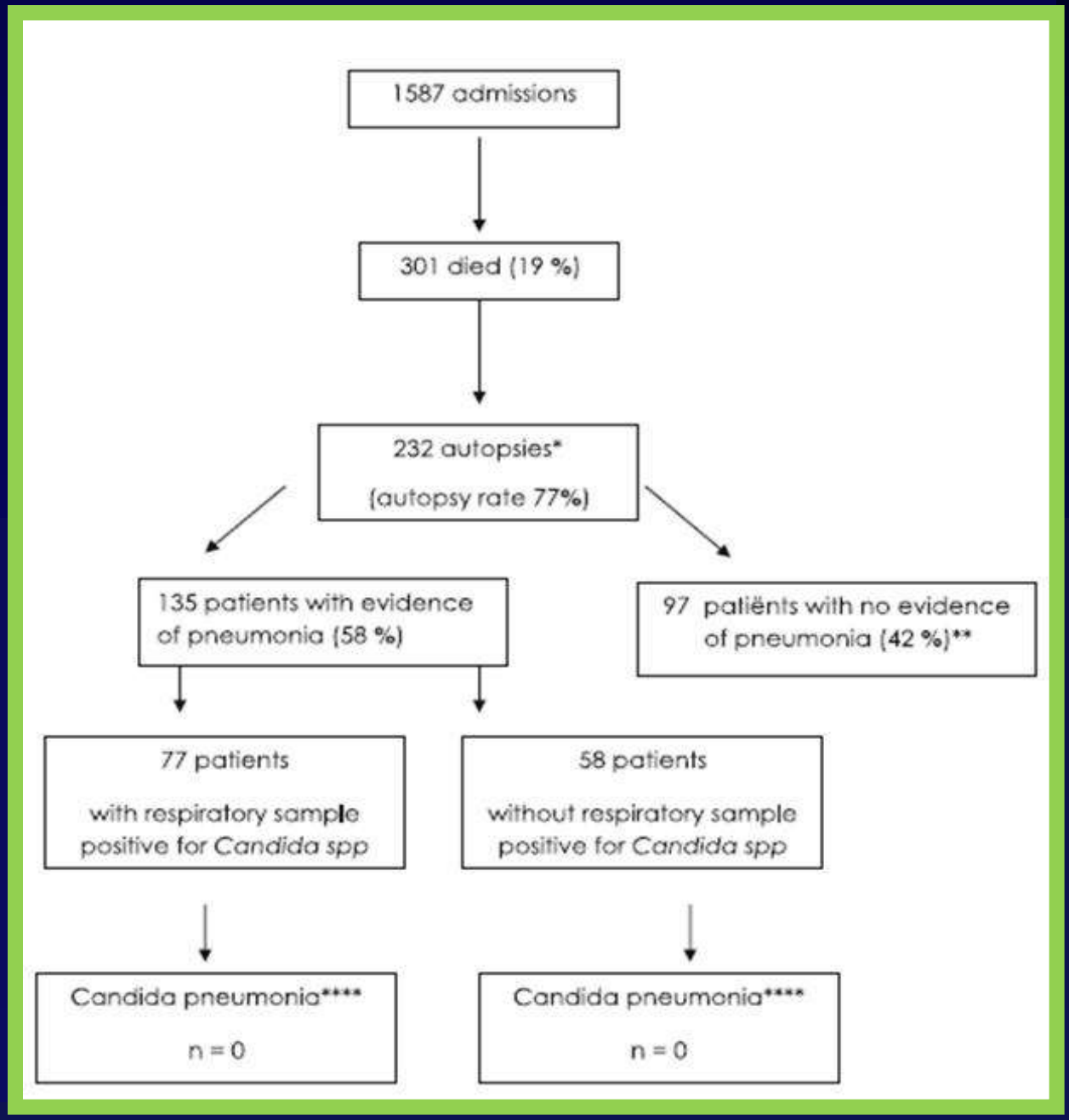
Andrea Cortegiani[1*], Giovanni Misseri[1], Mariachiara Ippolito[1], Matteo Bassetti[2], Antonino Giarratano[1], Ignacio Martin-Loeches[3,4] and Sharon Einav[5]

- **Bakteremiye kıyasla kandidiemik hastalarda daha düşük PCT düzeyleri var** (16 çalışma)
- Ancak çalışmalarda elde edilen **kanıtlar yetersiz**
- Tedavi yaklaşımını değiştirecek **ayırt ettiricilik** düzeyi düşük

SOLUNUM Örneklerinde *Candida*

- Pnömoni etkeni olma ihtimali **son derece düşüktür**
- Oral ve solunum mukozasında kolonizasyon
- Balgam kültürü: tanı değeri çok düşük
- **BAL kültüründe kandida üremesi olursa:**
  - Nötropenik olmayan hastalarda PPV < %30

Azoulay et al, Intensive Care Med (2004) 30:1384–1389



Meersseman W, 2009

Intensive care medicine

KATETER İNFEKSİYONU

- **Kandida kateter infeksiyonuna işaret eden bulgular**
  - Kanda *C. parapsilosis* üremesi
  - Kateter – periferik kan kantitatif üreme farkı (5-10 kat)
  - Kateter – periferik kan üreme zamanı farkı (2 saat)
  - Kateterden TPN alıyor olmak

- **Enfekte kateter mutlaka çekilmeli**

Mermel, Clin Infect Dıs 2001

İDRARDA Kandida

- 861 kandidürisi olan vakada
  - Sadece %4 ü semptomatik
  - %90 Antibiyotik kullanımı var
  - %82 sinde üriner kateter var
  - Tedavisiz %75 inde kendiliğinden negatifleşmiş
  - Tedavi verildiğinde %50 negatifleşmiş
  - Kandidemi %1.3
  - Mortalite farkı yok

Carol A, CID 2000

Bazı Hasta Gruplarında Kandidüri İnsidansı

Table 1 Studies evaluating epidemiology of candiduria in different patient populations

Study	Study population and description	Definition of candiduria (cfu/ml)[a]	Frequency of Candiduria
Colodner et al. [1]	Prevalence of candiduria in urine samples from both community and hospitalized patients	$\geq 10^4$ women $\geq 5\times 10^3$ men	0.2% of all samples 1% of culture positive samples
Padawer et al. [4]	Prevalence of catheter-associated candiduria in hospitalized patients	$\geq 10^4$	19.49%
Alvarez-Lerma et al. [2]	Incidence of candiduria in intensive care unit patients hospitalized > 7 days	$\geq 10^4$	22%
Bougnoux et al. [11]	Incidence, of nosocomial candiduria in intensive care unit patients	$\geq 10^{4b}$	27.4/1000 admissions
Delgado et al. [6]	Incidence of candiduria in renal transplant recipients	$\geq 5\times 10^4$	3.4%
Denis et al. [7]	Incidence of candiduria in renal transplant recipients	$\geq 10^3$	2.3/100 person-year 4%
Safdar et al. [15]	Incidence of candiduria in renal transplant recipients	$\geq 10^3$	11%
Goetz et al. [8]	Occurance rate of candiduria in chronically catheterized patients with spinal cord injury	Not defined	17%
Esmailzadeh et al. [9]	Prevalence of candiduria in type 2 diabetes patients	$\geq 10^3$ $\geq 10^4$	10% 7%

[a]cfu/ml: colony forming unit per mililiter of urine

[b]Quantitative urine cultures were available in 61% of patients, and 86% of them had *Candida* growth of $\geq 10^4$ cfu/ml

Odabasi Z, World J Urology, 2019

İNTRA-ABDOMİNAL Kandidiyaz

- YBÜ ‘de kandidemiden sonra 2inci en sık invaziv kandidiyaz
- Heterojen hastalıklar grubu (peritonit, abse, pankreatit)
- **Tanı**: aşağıdakilerden en az biri olmalı
  - Cerrahi veya kateterle alınan **nekrotik veya pürülan** batın içi örnekte *Candida* üremesi veya mikroskopta görülmesi
  - Sekonder ve tersiyer peritoniti olan bir vakada başka bir patojen olmadan kanda *Candida* üremesi
  - Batına yerleştirilen drenaj kateterlerinden ilk 24 saat içinde alınan örnekte *Candida* üremesi

Bassetti M, Crit Care, 2019

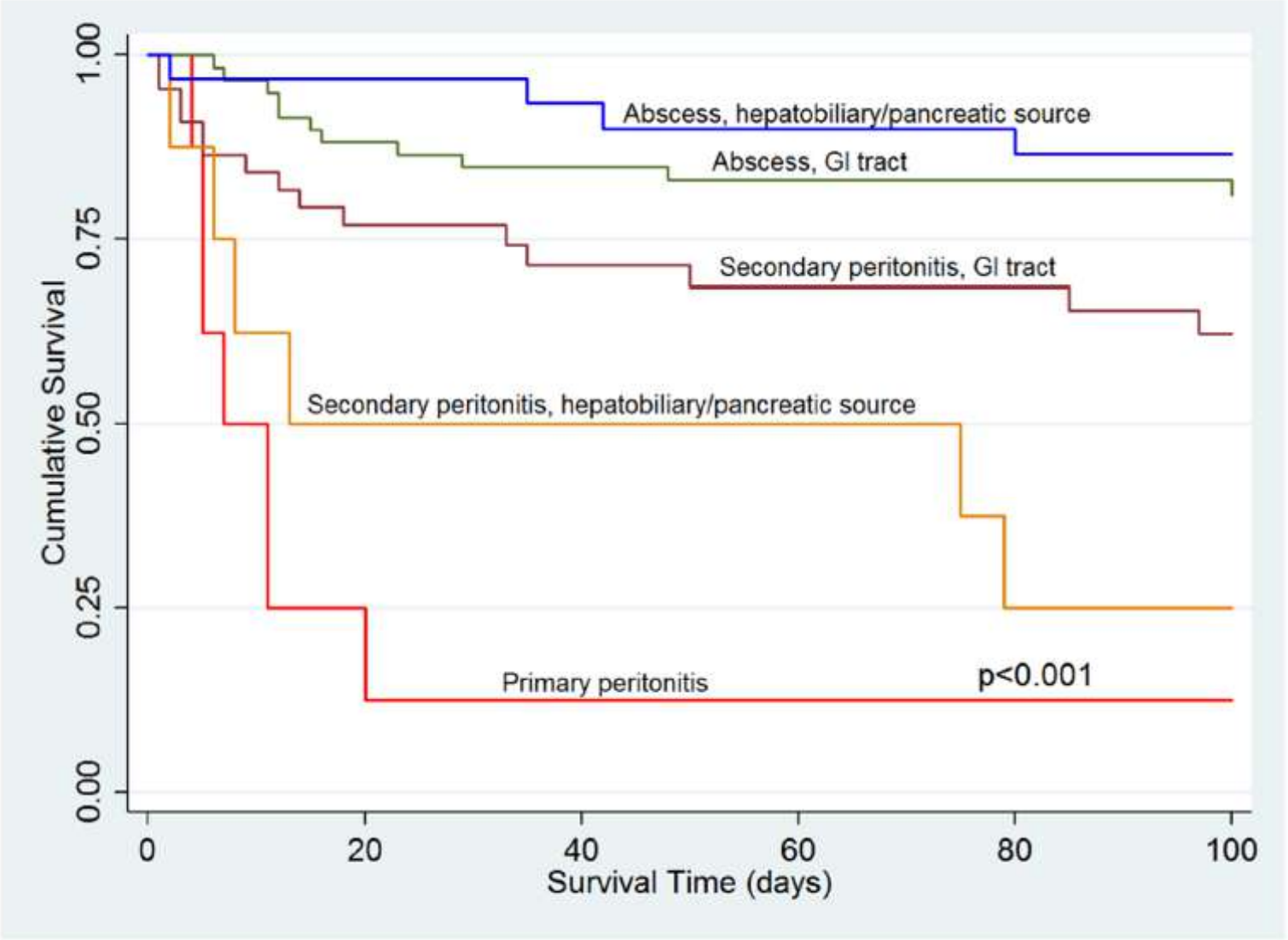


Fig 1. Survival analysis by type of intra-abdominal candidiasis.

Vergidis P, Plos One, 2016

KANDİDEMİ TEDAVİSİ

(NÖTROPENİK OLMAYAN HASTA)

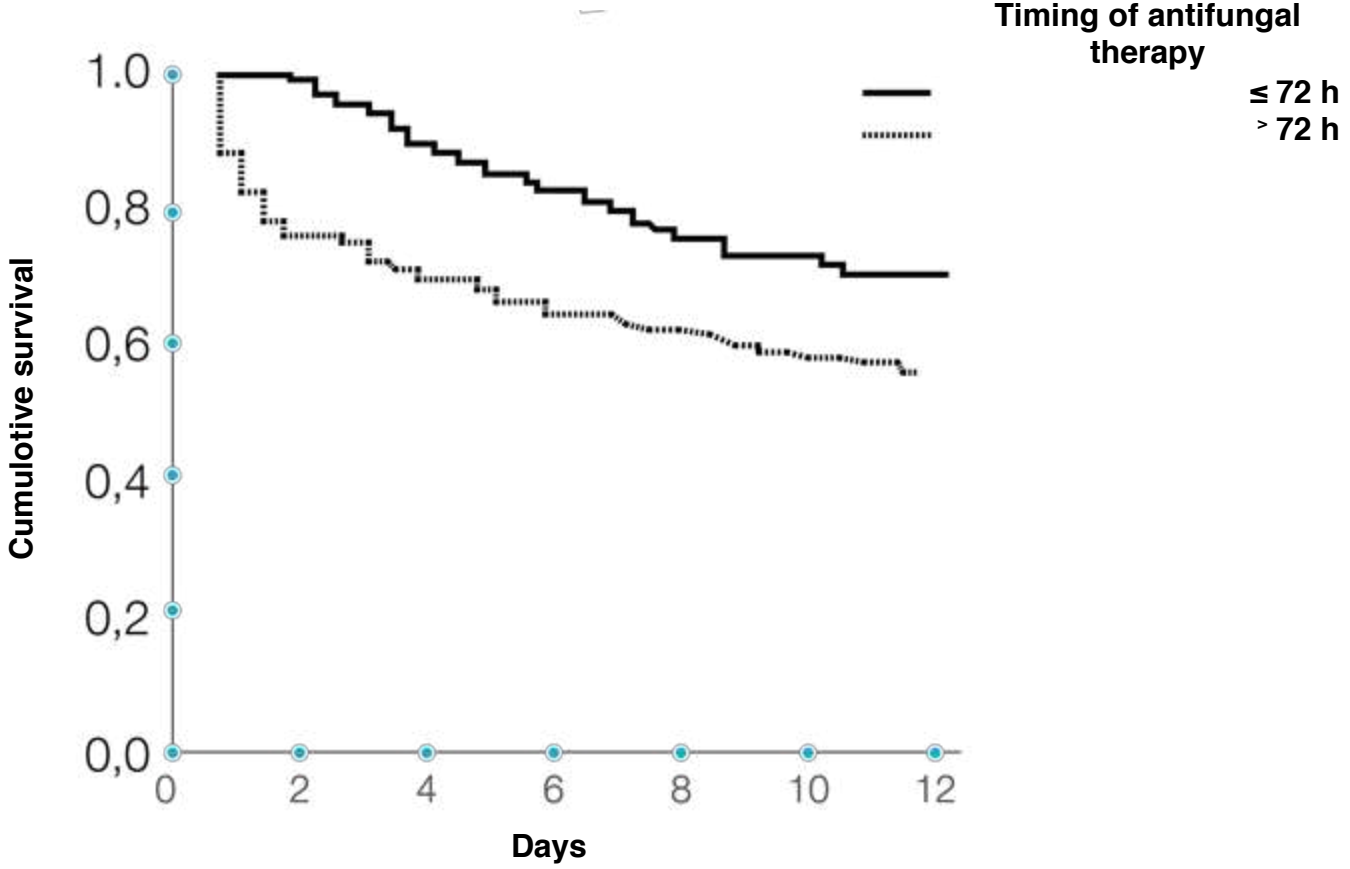
IDSA *Candida* Rehberi, Clin Infect Dis 2016

IDSA *Candida* Rehberi, Clin Infect Dis 2016

J Antimicrob Chemother 2012; **67**: 707–714
doi:10.1093/jac/dkr511 Advance Access publication 18 December 2011

Journal of Antimicrobial Chemotherapy

Timing of susceptibility-based antifungal drug administration in patients with *Candida* bloodstream infection: correlation with outcomes



Grim SA, J Antimicrob Chem 2012

	Drugs	Comments
First choice therapy	Anidulafungin Caspofungin Micafungin	Fungicidal activity against most *Candida* spp. Important anti-biofilm activity. Lack of penetration in eyes and central nervous system.
Second choice therapy	Fluconazole	Fluconazole has fungistatic activity and has limited activity againt *C. glabrata* and is inactive against *C. krusei*.
	L-AMB	Liposomal amphotericin B has a favourable toxicity profile, compared with other amphotericin formulations.
	Voriconazole	Voriconazole has a fungistatic activity. Reported activity also against *Candida glabrata* and *Candida krusei*. TDM should be considered.
Other	ABLC	Limited clinical data about efficacy and safety of ABLC.

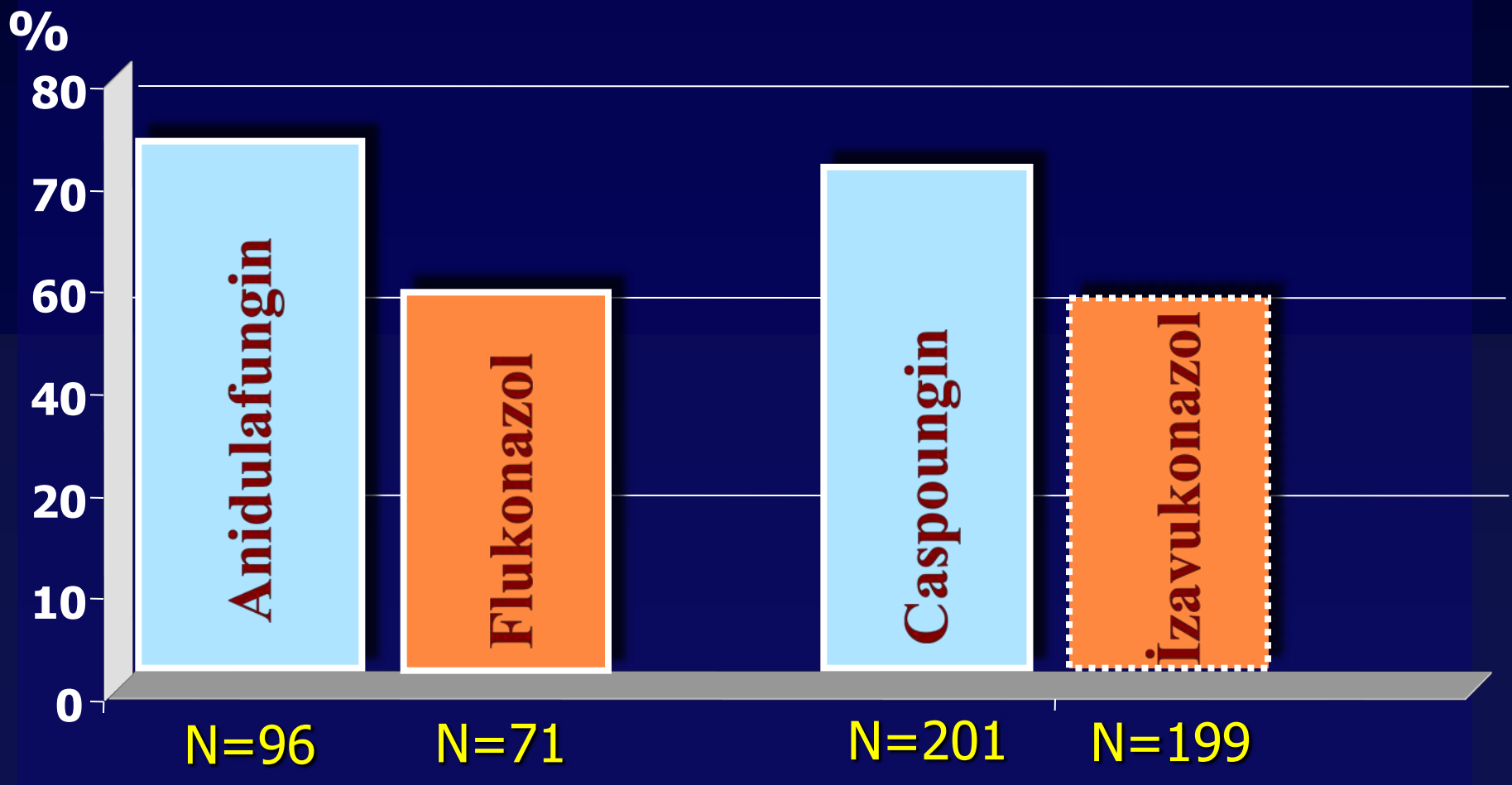
Bassetti M, Hosp Pract, 2018

Kandidemi Tedavisi – Nötropenik Olmayan hastalar

- Ekinokandinler
  - Caspofungin
  - Micafungin
  - Anidulafungin
- Fluconazol 800 mg yükleme – 400 mg idame

IDSA *Candida* Rehberi, Clin Infect Dis 2016

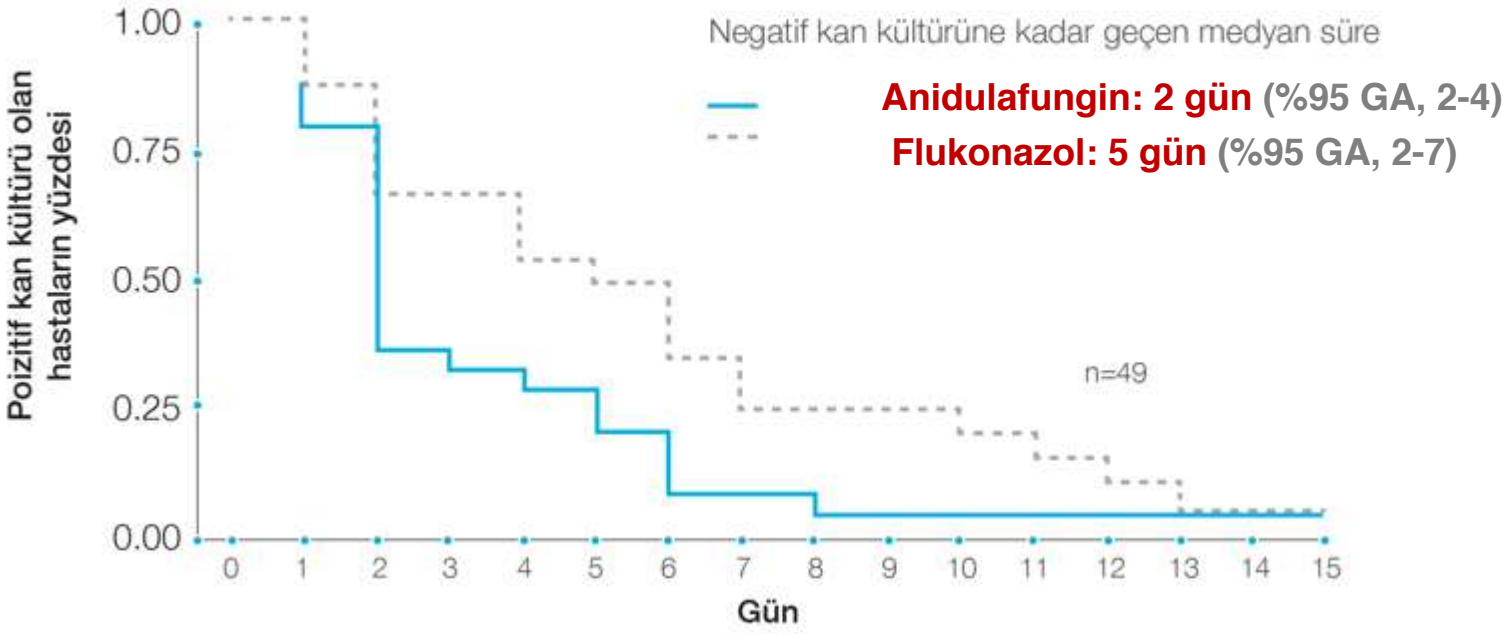
İnvaziv Kandidiyazda Ekinokandin vs Azol Çalışmaları



Reboli Çalışması / *C. albicans* Alt Analizi

Randomize, çift kör, çok merkezli Reboli çalışmasında sadece *C. albicans* saptanan 135 hastanın analizi

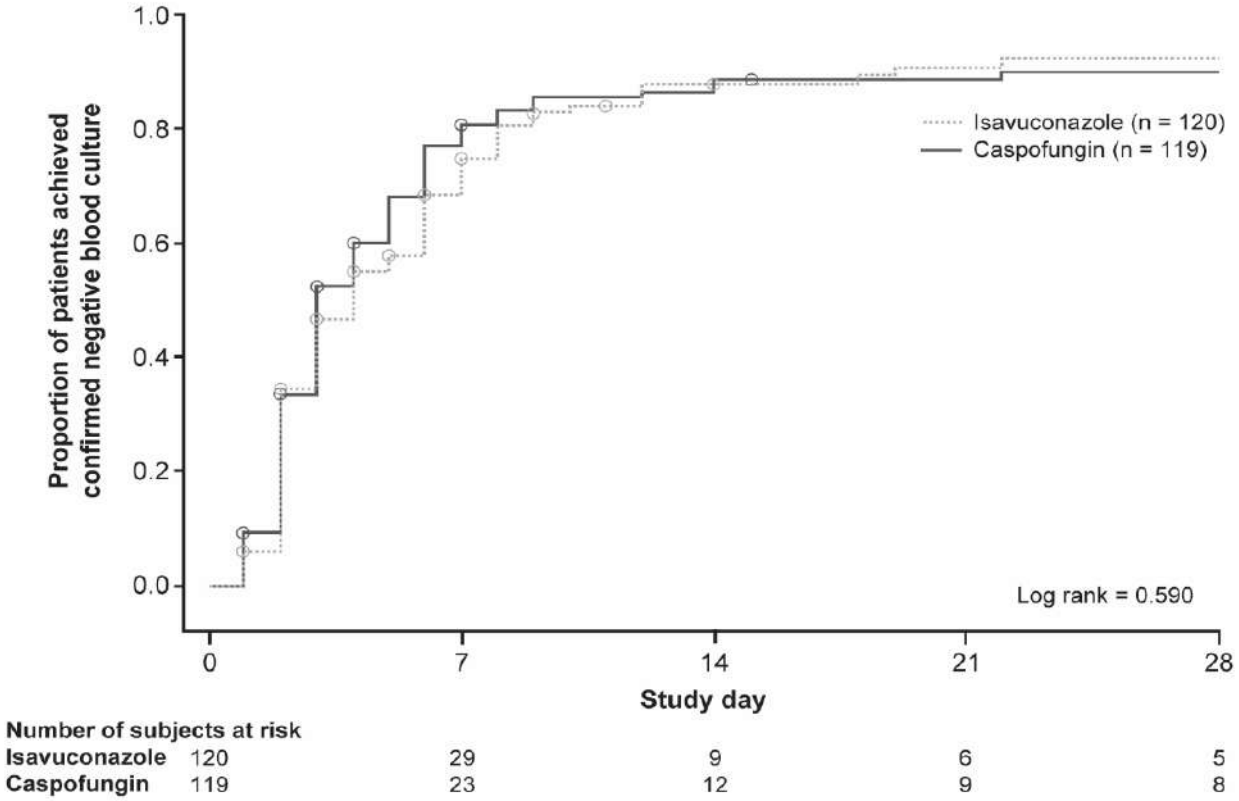
İlk negatif kan kültürüne kadar geçen süre - Kaplan Meier analizi



- **Anidulafungin, flukonazole göre *Candida* 'yı kandan daha hızlı temizler.**

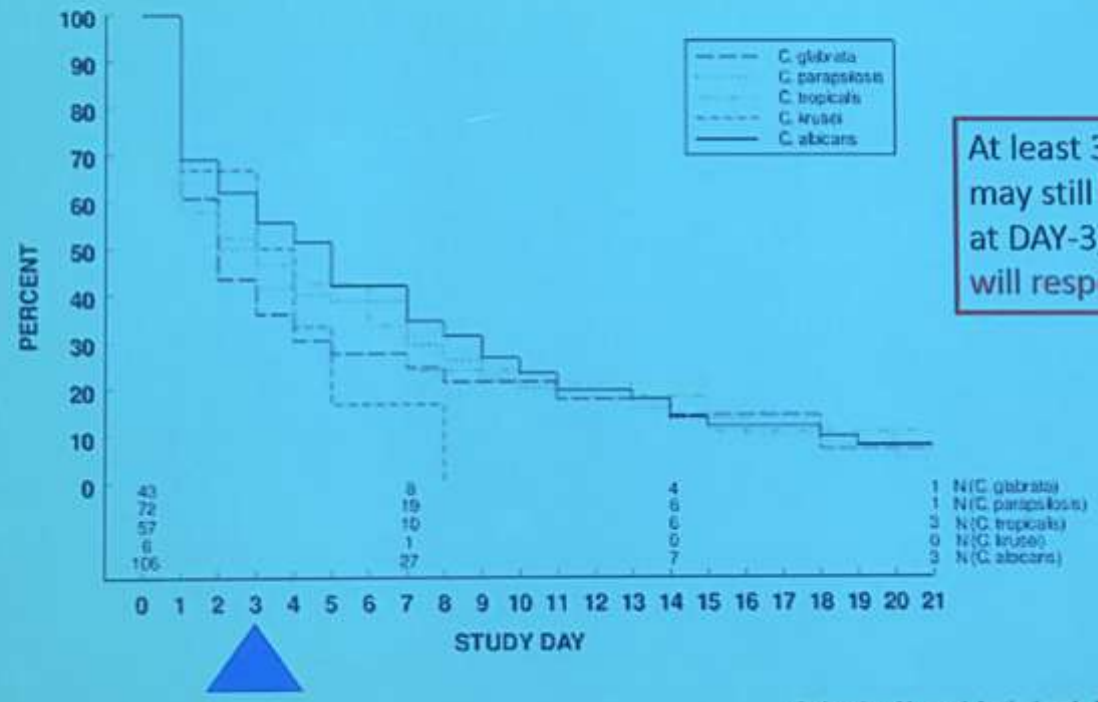
Referans: Reboli A, et al. BMC Infect Dis. 2011;11:261.

Kullberg, Flu vs Isavuc: Kültür negatifleşme süreleri



Kullberg J, CID, 2019

Kaplan-Meier curves of patients with *Candida sp:* Time to get first negative blood culture after therapy with CASPOFUNGIN



At least 30% of patients may still have a positive culture at DAY-3, and 70% of them will respond to therapy!

Colombo AL et al Antimicrob Agents Chemother 54(5):1864-1871, 2010

Prevalence rate of Endocardites in large series of candidemia

Author, yeas	Local	Period	Centers/ Episodes	Rate
Schelenz,2003	Londres	2000-01	4/128	3,1%
Rodrigues,2006	Barcelona	2002-2003	1/24	4%
Colombo, 2006	**Brasil**	2003-04	8/712	1,1%
Cisterna, 2010	Madri	2008-09	17/984	1,7%
Ortega, 2011	Barcelona	1991-2008	11/529	2%
Rodrigues Hernandez,2011	Andalucia	2005-06	3/220	1,4%
Fernandez-Cruz,2015*	Madri	2007-12	11/263	4,2%
Bassetti, 2019	Europe (ICUs)	2015-2016	23/330	2%

Rodrigues-Hernandez, et al. 2011;29(5):328
Fernandez-Cruz et al. Eur J Clin Microbiol Infec Dis.2015;34(8):1543-9
Rodrigues D, et al. Pedi Infect Dis J;2006;25:224

Colombo et al. J Clin Microb. 2006;44(8):2816
Cisterna el Al. J Clin Microbiol.2010;48(11):4200
Ortega et al. J Hosp Infect.2011;77:157
Bassetti et al. Critical Care (2019) 23:219

Ekinokandinler: Siroz ve KBY'de doz ayarlaması

Ekinokandin	Child A	Child B	Child C	Akut Kc yetersizliği	GFR <50
Caspofungin	**Hayır**	35mg	Çalışma yok	Çalışma yok	**Hayır**
Anidulafungin	**Hayır**	**Hayır**	**Hayır**	**Hayır**	**Hayır**
Mikafungin	**Hayır**	**Hayır**	**Hayır**	**Hayır**	**Hayır**

Ekinokandinlerin Doku Penetrasyonları

- Bir çok dokuda oldukça iyi konsantre olmakla beraber
- Ekinokandin konsantrasyonunun düşük olduğu dokular:
  - Beyin
  - Göz
  - İdrar

Kandidemi Tedavisi

- **Tüm *Candida* izolatlarında azol duyarlılığı bakılması kuvvetle önerilir**
  - Ekinokandin duyarlılığı ise şu durumlarda önerilir:
    - **Daha önceden ekinokandin kullanım öyküsü**
    - ***C parapsilosis*** ve ***C glabrata*** üremesi

IDSA *Candida* Rehberi, Clin Infect Dis 2016

Kandidemi Tedavisi
Ekinokandin → Azol değişimi

- Hastanın kliniği **stabil,**
- Üreyen izolat flukonazole **duyarlı ve**
- Kontrol kan kültürleri **negatifleşti** ise
- **5-7 günlük ekinokandin kullanımı sonunda** yapılabilir

IDSA *Candida* Rehberi, Clin Infect Dis 2016

Kateteri Çekilemeyen Hastada Ekinokandinle Devam Et

Consensus statement

- The panel recommends de-escalating from an echinocandin to fluconazole when the patient is clinically stable and the isolate is susceptible to fluconazole (Strong recommendation, moderate quality of evidence.)
- Echinocandins should not be de-escalated if central venous catheter or any other foreign material has not been removed. This recommendation is particularly pertinent to cases with an intravascular catheter that cannot be removed or if an intravascular device (e.g. pacemaker) must be left in place. (strong recommendation, moderate quality of evidence).
- The panel recommends that antifungal treatment should be stopped in patients with suspected (but not proven) IC with negative blood cultures and/or other negative culture specimens taken from suspected infectious foci before starting antifungal therapy (best practice statement).

Martin-Loeches I, Intensive Care Med, 2019

J Antimicrob Chemother
doi:10.1093/jac/dkx116

Journal of Antimicrobial Chemotherapy

Efficacy of anidulafungin in 539 patients with invasive candidiasis: a patient-level pooled analysis of six clinical trials

Bart Jan Kullberg[1]*, José Vasquez[2], Piroon Mootsikapun[3], Marcio Nucci[4], José-Artur Paiva[5], Jorge Garbino[6], Jean Li Yan[7], Jalal Aram[7], Maria Rita Capparella[8], Umberto Conte[7], Haran Schlamm[7], Robert Swanson[7] and Raoul Herbrecht[9]

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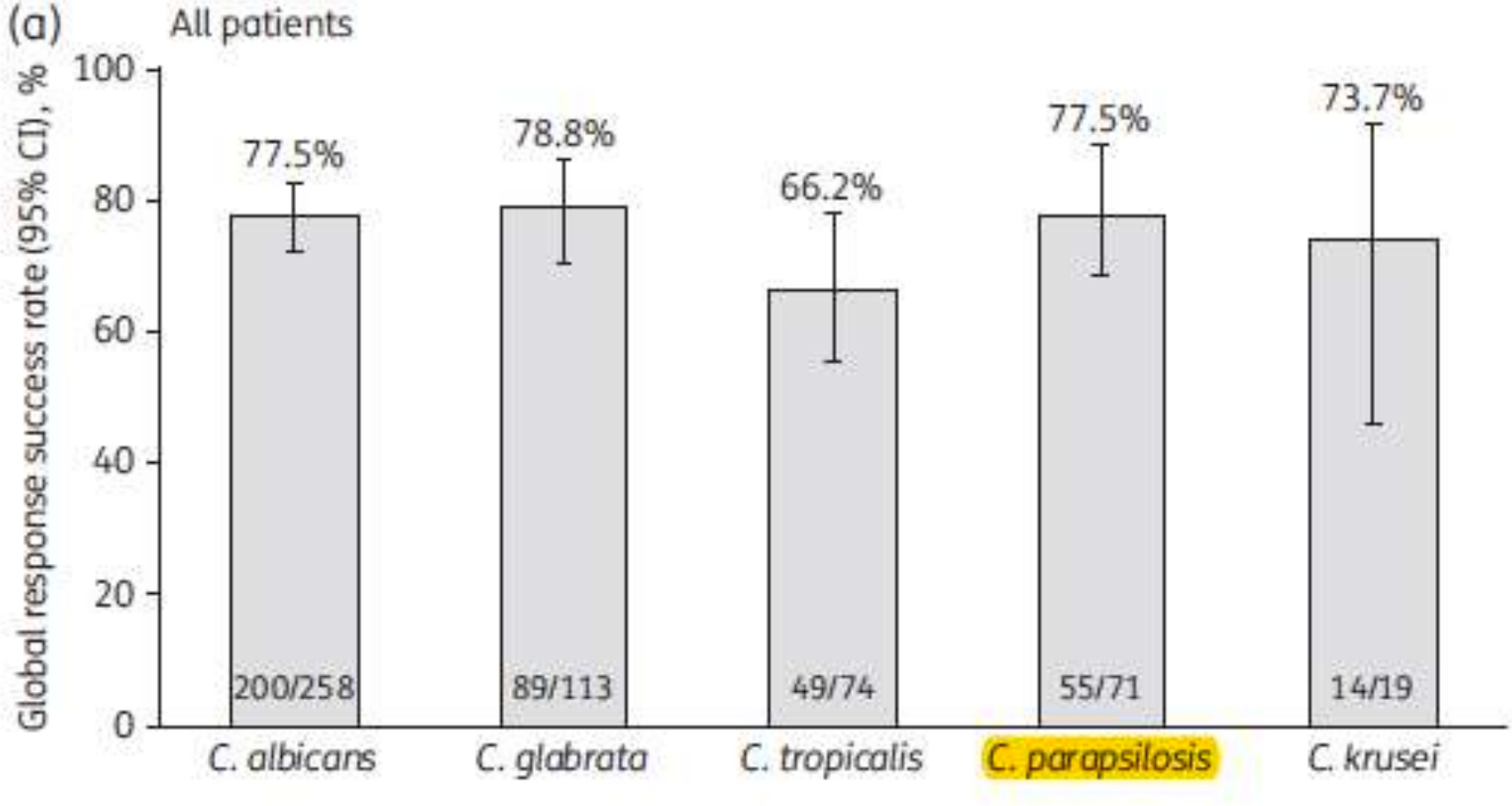
Received 23 December 2016; returned 10 February 2017; revised 18 March 2017; accepted 20 March 2017


(a)
All patients
Global response success rate (95% CI), %
100
80
60
40
20
0
77.5%
78.8%
66.2%
77.5%
73.7%
200/258
89/113
49/74
55/71
14/19
C. albicans
C. glabrata
C. tropicalis
C. parapsilosis
C. krusei

MAJOR ARTICLE

Initial Use of Echinocandins Does Not Negatively Influence Outcome in *Candida parapsilosis* Bloodstream Infection: A Propensity Score Analysis

Mario Fernández-Ruiz,[1] José María Aguado,[1] Benito Almirante,[2,3] David Lora-Pablos,[4,5] Belén Padilla,[6] Mireia Puig-Asensio,[2,3] Miguel Montejo,[7] Julio García-Rodríguez,[8] Javier Pemán,[9] Maite Ruiz Pérez de Pipaón,[10] and Manuel Cuenca-Estrella[11]; for the CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI[a]

[1]Unit of Infectious Diseases, Hospital Universitario "12 de Octubre," Instituto de Investigación Hospital "12 de Octubre," Madrid; [2]Department of Infectious Diseases, Hospital Universitari "Vall d'Hebron," and [3]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona; [4]Unit of Clinical Research, Hospital Universitario "12 de Octubre," Instituto de Investigación Hospital "12 de Octubre," Madrid; [5]Centro de Investigatión de Epidemiología y Salud Pública, and [6]Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario "Gregorio Marañón," Madrid; [7]Unit of Infectious Diseases, Hospital Universitario de Cruces, Barakaldo; [8]Department of Microbiology, Hospital Universitario "La Paz," Madrid; [9]Department of Microbiology, Hospital Universitario "La Fe," Valencia; [10]Department of Microbiology, Hospital Universitario "Virgen del Rocío," Sevilla, and [11]Department of Mycology, Spanish National Center for Microbiology, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain

(See the Editorial Commentary by Reboli on pages 1422–3.)

J Antimicrob Chemother 2016; **71**: 3536–3539
doi:10.1093/jac/dkw305 Advance Access publication 27 July 2016

Journal of Antimicrobial Chemotherapy

Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidaemia due to *Candida parapsilosis*: a retrospective observational cohort study of the Mycoses Study Group (MSG-12)

Kathleen Chiotos[1–3]*, Neika Vendetti[1,3], Theoklis E. Zaoutis[1,3,4], John Baddley[5,6], Luis Ostrosky-Zeichner[7], Peter Pappas[5] and Brian T. Fisher[1,3,4]

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Received 1 May 2016; returned 24 May 2016; revised 17 June 2016; accepted 28 June 2016

Candida parapsilosis

Multivariate propensity score analysis of 307 *C. parapsilosis* episodes in the Premier Perspective Database, 2009–2013[1] (Mycoses Study Group MSG-12)

Potential determinants of failure	Echinocandin N=181 (59%)	Fluconazole N=126 (41%)	After IPTW
Age (median)	60	60	2.4
Gender (m, %)			
Race (black, %)			
ICU / ICU resources (e.g., arterial line)			
Vasopressors (%)			
Year of candidemia (2009-2013)			
Charlson comorbidity score (median)			
Length of stay (median, d)			
Length of stay before candidemia onset			
Antifungal prophylaxis (%)			
Healthcare-onset candidemia (%)			
Empiric antifungals (%)			

30 gün sonunda mortalite

	Echinocandin	Fluconazole
Crude mortality	9.9%	9.5%
Odds ratio (95%CI)	1.05 (0.49, 2.26)	
Propensity score model weighted logistic regression		
Odds ratio (95%CI)	0.82 (0.33, 2.07)	

[1]Adult patients with candidemia, surviving 14 days after BC sample growing *C. parapsilosis* only, who received fluconazole or echinocandin monotherapy

[2]Standardized differences after inverse probability of treatment weighting (IPTW), included in final propensity score model. PCVC, not applicable

Chitasombat M, et al. / Antimicrob Chemother 2015; 71: 3136–39

Kandidemi Tedavi Süresi

- **Komplike edici bir durum yoksa** son kan kültürü negatifliğinden sonra **2 hafta** verilir
- **Komplike enfeksiyonlarda** bulgular düzelene kadar daha uzun verilebilir

IDSA *Candida* Rehberi, Clin Infect Dis 2016

Göz dibi muayenesi !!!

- **Tüm kandidemi vakalarında İlk 1 hafta içerisinde**
- **Koryoretinit varlığında: IV flukonazol veya vorikonazol**
  - **Dirençli izolatlarda Amfoerisin B**
  - **Maküler veya vitreal tutulum** varsa **intravitreal** AmB veya vorikonazol yapılır
  - Tedavi süresi en az 4-6 hafta

IDSA *Candida* Rehberi, Clin Infect Dis 2016

Kandidiemi ve Santral kateter varlığı

- Kandidemi sebebi kateter olarak düşünülüyorsa mümkün olan en kısa sürede kateter çekilmelidir
- Mortalite üzerine olumlu etkisi var
- Ekinokandinlerin biofilm etkisi önemli

IDSA *Candida* Rehberi, Clin Infect Dis 2016

İntra abdominal Kandidiyaz Tedavisi

- **Ampirik antifungal tedavi önerilir:**
  - Klinik kanıt varsa
  - Ciddi risk faktörleri varsa
    - Abdominal cerrahi
    - Anastomoz kaçağı
    - Nekrotizan pankreatit
- **Yeterli drenaj, debridman ile kaynak kontrolü sağlanmalı**

IDSA *Candida* Rehberi, Clin Infect Dis 2016

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

The Gastrointestinal Tract Is a Major Source of Echinocandin Drug Resistance in a Murine Model of *Candida glabrata* Colonization and Systemic Dissemination

Kelley R. Healey, Yoji Nagasaki, Matthew Zimmerman, Milena Kordalewska, Steven Park, Yanan Zhao, David S. Perlin

Public Health Research Institute, New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark, New Jersey, USA

Caspofungin 'in GİS penetrasyonu zayıf,
GIS 'te *C glabrata ile* ekinokandin direnci gelişebilir

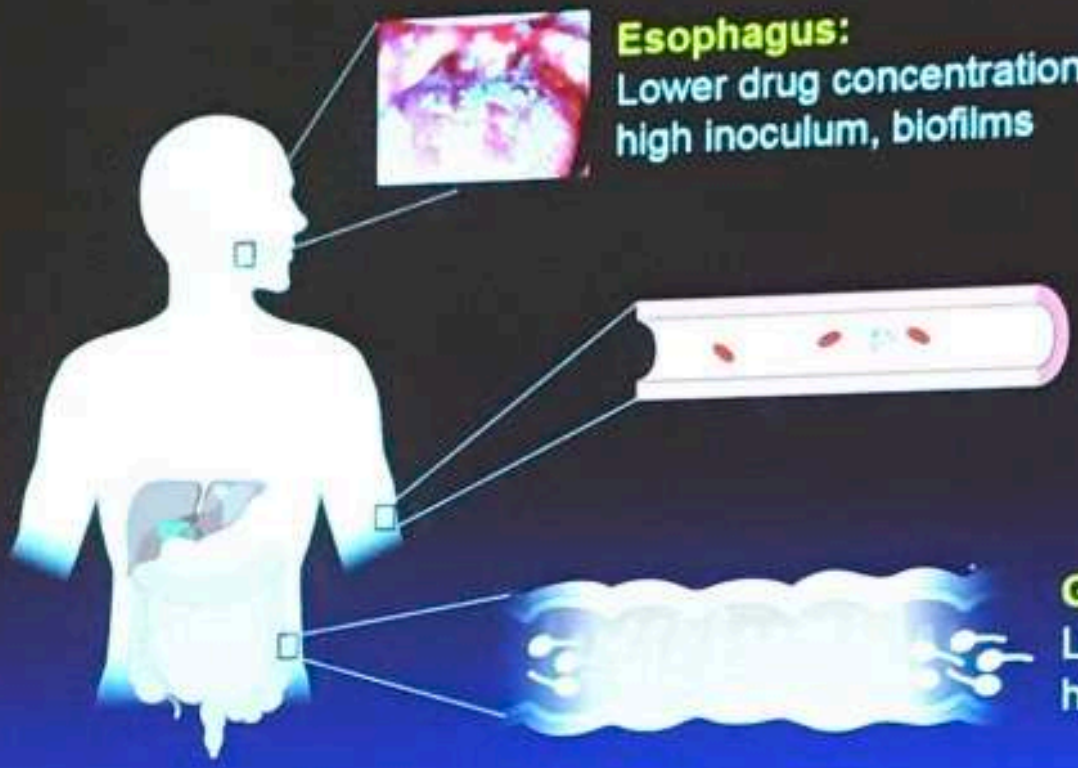
ABSTRACT *Candida* species are a part of the human microbiome and can cause

gin resulted in no reduction in fecal burdens, organ breakthrough rates similar to control groups, and resistance rates (0 to 10%) similar to those reported clinically. Treatment with 20 mg/kg caspofungin initially reduced burdens, but a rebound following 5 to 9 days of treatment was accompanied by high levels of resistance (*FKS1*/*FKS2* mutants). Although breakthrough rates decreased in this group, the same *FKS* mutants were recovered from organs. In an attempt to negate drug tolerance that is critical for resistance development, we cotreated mice with daily caspofungin and the chitin synthase inhibitor nikkomycin Z. The largest reduction (3 log) in GI burdens was obtained within 3 to 5 days of 20 mg/kg caspofungin plus nikkomycin treatment. Yet, echinocandin resistance, characterized by a novel Fks1-L630R substitution, was identified following 5 to 7 days of treatment. Therapeutic caspofungin plus nikkomycin treatment left GI burdens unchanged but significantly reduced organ breakthrough rates (20%; $P < 0.05$). Single-dose pharmacokinetics demonstrated low levels of drug penetration into the GI lumen posttreatment with caspofungin. Overall, we show that *C. glabrata* echinocandin resistance can arise within the GI tract and that resistant mutants can readily disseminate upon immunosuppression.

The gastrointestinal tract is a major source of echinocandin drug resistance in a murine model of *Candida glabrata* colonization and systemic dissemination. Antimicrob Agents Chemother 61:e01412-17. https://doi.org/10.1128/AAC.01412-17.

Address correspondence to Kelley R. Healey, krh75@njms.rutgers.edu, or Yanan Zhao, zhaoy1@njms.rutgers.edu.

Where do we look for echinocandin resistance?



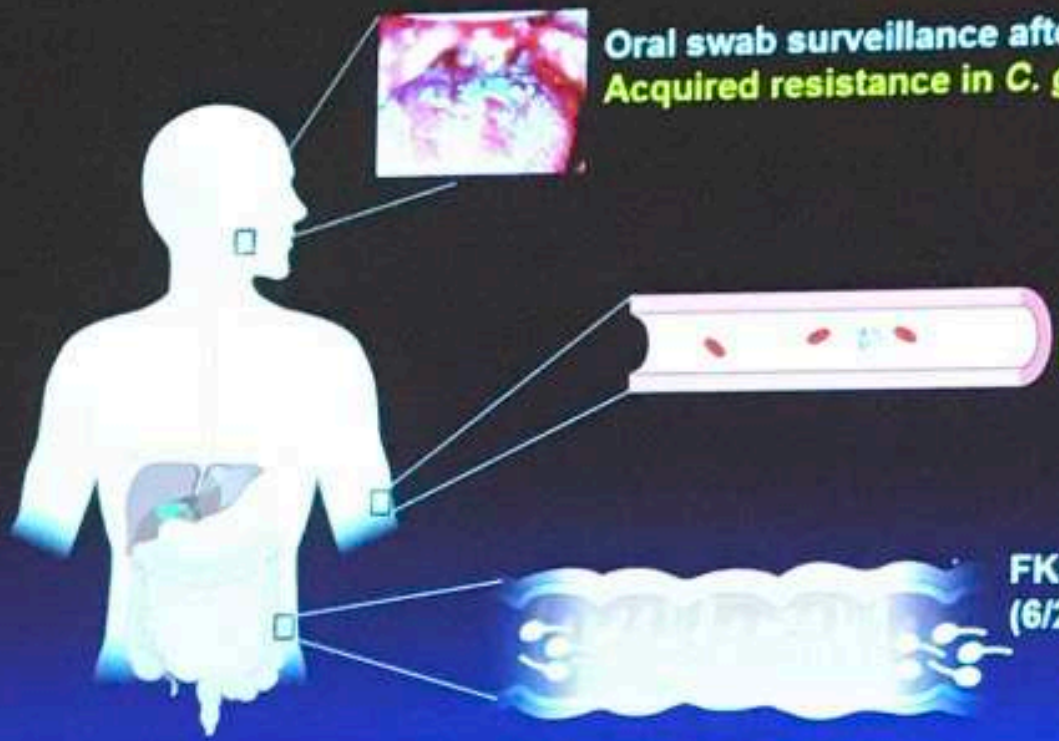
Esophagus:
Lower drug concentrations, high inoculum, biofilms

Bloodstream:
High drug concentrations, low inoculum

Gut:
Low drug concentrations, high inoculum, biofilms?

Healey et al. *Antimicrob Agents Chemother* 2017;61(12).

Where do we look for echinocandin resistance?



Oral swab surveillance after ≥ 7 days of echinocandins[2]
Acquired resistance in *C. glabrata* 21.6%

SENTRY 2006-2016, single center studies[1,2]
Echinocandin resistance rate: 3-12%

FKS mutant *Candida* isolates detected in 24% (6/25) patients exposed to echinocandins[4,5]
- *C. glabrata* 29%
- *C. albicans* 14%

[1]Pfaller M et al. *Open Forum Infect Dis* 2019;6 (Supplement_1):S79–94.
[2]Alexander et al. Clin Infect Dis 56:1724-32.
[3]Jensen RH, Johansen HK, Soes LM, et al. *Antimicrob Agents Chemother.* 2016;60(3):1500-1508.
[4]Shields RK, Nguyen MH, Press EG, Clancy CJ. *Antimicrob. Agents Chemother.* 2014;58(12):7601-7605.
[5]Prigent et. al. *Antimicrobial Agents Chemother.* 2016; Nov 15, 2016.

Nötropenik Olmayan Bir YBÜ Hastasında Kandidemi Şüphesine Yönelik Ampirik Tedavi

- **Septik şok veya nedeni belli olmayan ateşle beraber**
  - Kandida enfeksiyon risk faktörleri
  - Kandida enfeksiyon belirteçlerinin pozitifliği
  - **Nonsteril bölgelerde kandida** üretilmesi
- **İlk tercih ekinokandinler**
  - Azol öyküsü yok, direnç düşük ise **flukonazol** verilebilir
- Klinik yanıt varsa 2 hafta tedavi verilir
- **Yanıt yok, destekleyici bulgu yoksa 4-5 günde kesilir**

IDSA Kandida Rehberi, Clin Infect Dis 2016

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

The EMPIRICUS Randomized Clinical Trial

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Editorial

Supplemental content

IMPORTANCE Although frequently used in treating intensive care unit (ICU) patients with sepsis, empirical antifungal therapy, initiated for suspected fungal infection, has not been shown to improve outcome.

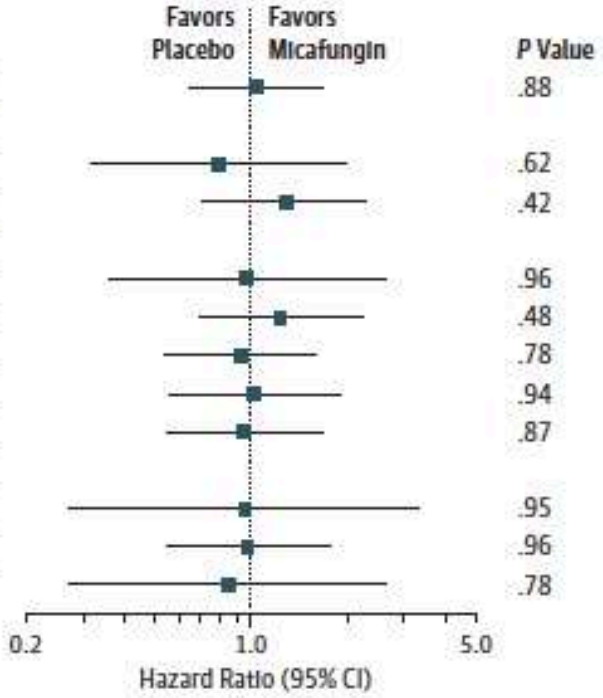
OBJECTIVE To determine whether empirical micafungin reduces invasive fungal infection (IFI)–free survival at day 28.

DESIGN, SETTING, AND PARTICIPANTS Multicenter double-blind placebo-controlled study of 260 nonneutropenic, nontransplanted, critically ill patients with ICU-acquired sepsis, multiple *Candida* colonization, multiple organ failure, exposed to broad-spectrum antibacterial agents, and enrolled between July 2012 and February 2015 in 19 French ICUs.

INTERVENTIONS Empirical treatment with micafungin (100 mg, once daily, for 14 days) (n = 131) vs placebo (n = 129).

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-β-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78



Timsit JF, JAMA, 2016

Kandida Üriner Sistem Enfeksiyonlarının Tedavisi

Table 3 Summary of the treatment approaches in patients with asymptomatic candiduria

Conditions	Antifungal treatment	Recommendations
Detection of candiduria in an asymptomatic non-catheterized patient	No	Repeating urine culture 1–2 days later to rule out contamination
Asymptomatic patients with candiduria and urinary indwelling catheters	No	Change catheter Repeat urine culture on next day
Persistence of candiduria after changing catheter in an asymptomatic patient	No	Evaluate and remove predisposing factors: Remove catheter if possible Control blood sugar Treat obstruction Stop antibiotics Urinary system imaging may be considered
Asymptomatic candiduria patients without any known risk factors	No	Follow with urine cultures Most of them resolve within weeks to months
Asymptomatic candiduria in renal transplant recipients	No	Try to remove predisposing factors Antifungal treatment is not recommended
Asymptomatic candiduria patients with high risk of developing candidemia	Yes	Neutropenic patients Patients exposed to urological manipulations Very low-birth-weight infants (< 1500 g)
Asymptomatic candiduria in patients undergoing urological manipulations	Yes	Fluconazole 400 mg daily, or 6 mg/kg or deoxycholate Amphotericin B 0.3–0.6 mg/kg daily, several days before and after the procedure

Odabasi Z, World J Urology, 2019

Kandida Üriner Sistem Enfeksiyonlarının Tedavisi

- Sistit ve piyelonefrit
  - Flukonazol öncelikle tercih edilir
  - Azol direnci varsa Amfoterisin B
  - Ekinokandinler, vorikonazol, posakonazol alt üriner sisteme geçişi çok zayıftır

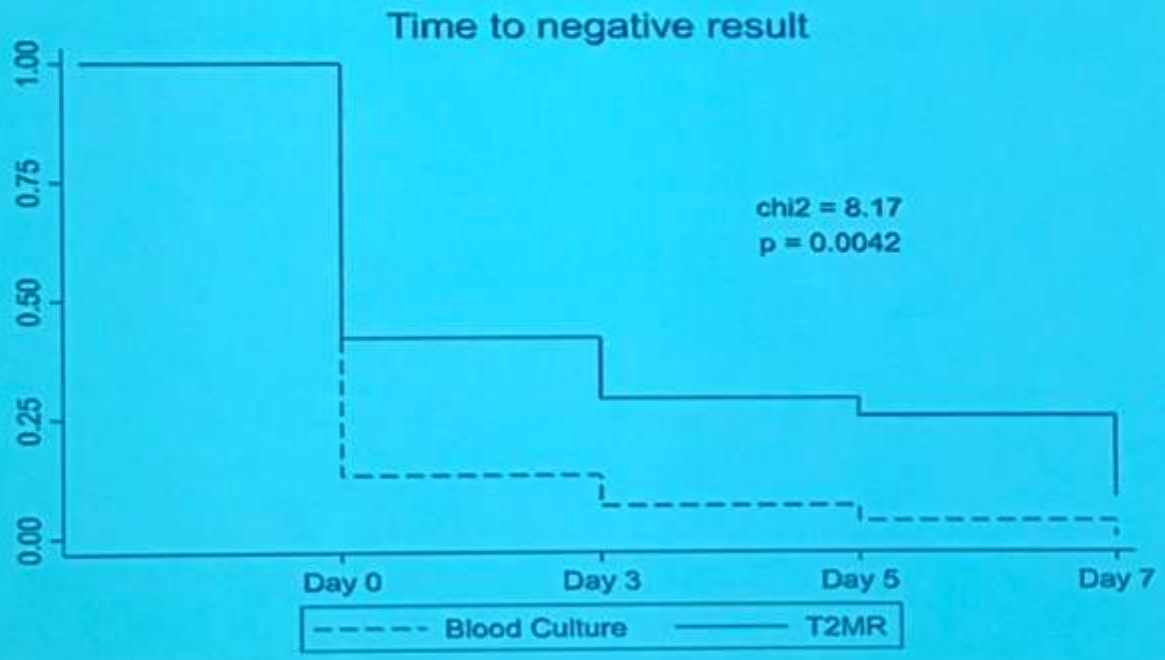
Yanıt Beklenen Sorular

- Persistan kandideminin tanımı nedir?
  - >3 gün >5 gün >10 gün >14 gün…
- Ne zaman farklı bir antifungale geçilmeli?
- Kombinasyon tedavisinin yeri nedir?
- Santral kateter kaç kere değiştirilebilir?
- Derin doku enfeksiyonlarının takibi nasıl yapılmalı, tedavi süresi nasıl ayarlanmalı?
- Ekinokandin direnci düşük ama neden hala başarısızlıklar görülebiliyor?

Kanda üreme olmadığı halde T2 MR pozitif

Efficacy of T2 Magnetic Resonance Assay in Monitoring Candidemia after Initiation of Antifungal Therapy

Kaplan Meier Diagram for the first week of antifungal therapy in 31 candidemic patients



Mylonakis E et al, J Clin Microbiol 2018 Mar 26;56(4). pii: e01756-17.

Ekinokandinlere yanıtsızlığın muhtemel nedenleri

- Tanım???
- Klinik başarısızlık vs Mikrobiyolojik yanıtsızlık ???

- Altta yatan hastalığın kontrol edilememesi
- Ağır hastalık varlığı ve risk faktörlerinin devamı
- Kaynak kontrolü
  - Abse
  - Kateter (her zaman çıkarmak m,mk,n olamayabiliyor)
  - Yabancı cisim

Ekinokandinlere yanıtsızlığın muhtemel nedenleri

- Derin doku enfeksiyonu
- PK / PD
- İzolatın virulansı
- İntrensek ya da edinilmiş direnç
- Endokardit, enfekte trombüs ?

AAC

Altered Micafungin Pharmacokinetics in Intensive Care Unit Patients

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AAC

Low but Sufficient Anidulafungin Expos

Marjolijn J. P. van Wanrooy,[a] Michael G. G. Rodgers,[b] Donald R. A. Uges,[a] J
Jos G. W. Kosterink,[a,e] Jan-Willem C. Alffenaar[a]

University of Gron
University Medica
Department of M
Pulmonary Disea
Division, Groning

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Candida türlerine etkili Yeni Antifungaller?

Fosmanogepix

Ibrexafungerp

Rezafungin

Low Caspofungin Exposure in Patients in Intensive Care Units

Kim C. M. van der Elst,[a]* Anette Veringa,[a] Jan G. Zijlstra,[b] Albertus Bolshuizen,[c] Rob Klont,[d] Petra Brummelhuis-Visser,[e] Donald R. A. Uges,[a] Daan J. Touw,[a] Jos G. W. Kosterink,[a,f] Tjip S. van der Werf,[g,h] Jan-Willem C. Alffenaar[a]

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-019-03477-3

ORIGINAL ARTICLE

Persistent Candidemia in adults: underlying causes and clinical significance in the antifungal stewardship era

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Received: 29 October 2018 / Accepted: 2 January 2019

Persistan kandidemi > 5 gün

Abstract

To investigate the causes and the clinical significance of persistent candidemia (PC) in adults diagnosed in a tertiary hospital with an active antifungal stewardship program. Retrospective cohort including all adults with candidemia from 2010 to 2018. PC was defined as any positive follow-up blood culture (BC) obtained ≥ 5 days from the first BCs yielding the same *Candida* species. PC was detected in 35/255 (13.7%) patients. There were no differences regarding antifungal adequacy in PC vs. non-PC (94.3% vs. 82.3%, $p = 0.084$) and primary source control (63.3% vs. 76.4%, $p = 0.172$) at the time of the follow-up BCs. The average time until source control (2 [0–37] vs. 2 days [0–44], $p = 0.311$) or adequate antifungal treatment (2 [0–26] vs. 2 days [− 2–10], $p = 0.748$) was similar. Patients with PC had more non-ocular complications (31.4% vs. 10.5%, $p = 0.002$). No impact on 30-day mortality was observed (31.4% vs. 22.3%, $p = 0.238$). The only independent factor associated with PC was to have a previously undetected site of infection [OR 4.28, 95%CI (1.77–10.34), $p = 0.001$]. Persistent candidemia was not associated with inadequate or delayed therapeutic management, nor higher 30-day mortality rates. Timely screening and control of unexpected infection sources are encouraged to shorten hospitalization and improve patient care.

Keywords Persistent candidemia · Antifungal stewardship · Mortality · Candidemia

Tedavi uygunluğu, zamanlaması, kateter çekilme süreleri ve mortalite farkı yok

Persistan grupta daha fazla göz dışı metastatik tutulum

Persistan vakalarda mutlaka odak araştırılmalı

- Septik tromboflebit
- Endokardit
- Diğer organlar: KC, dalak, akciğer

Echocardiogram	196 (89.1)	32 (91.4)	0.779
Doppler ultrasound of deep vessels	26 (11.8)	12 (34.3)	0.002
Complications, *n* (%)			
Ocular candidiasis	26 (11.8)	4 (11.4)	1
Non-ocular complications	23 (10.5)	11 (31.4)	0.002
Septic thrombophlebitis	13 (5.9)	5 (14.3)	0.082
Endocarditis	4 (1.8)	3 (8.6)	0.056
Other organs	6 (2.7)	3 (8.6)	0.066
Outcomes, *n* (%)			
ICU admission due to candidemia	21 (9.5)	6 (17.1)	0.231
30-day mortality	49 (22.3)	11 (31.4)	0.283
>30-day mortality[b]	68 (30.9)	15 (42.9)	0.177
Hospital length of stay, median in days (IQR)	28 (5–254)	41.5 (8–112)	0.021

AF antifungal, *BC* blood culture, *ICU* intensive care unit

[a] Source control was defined as "early" when performed within 48 h from the initial antifungal treatment

[b] Death at any time after 30 days during hospitalization

Clinical characteristics and risk factors for mortality in adult patients with persistent candidemia

Seung Ji Kang[1], Seong Eun Kim[1], Uh Jin Kim[1], Hee-Chang Jang[1], Kyung-Hwa Park[1], Jong Hee Shin[2], Sook In Jung[1]

[1]Department of Internal Medicine, Chonnam National University Medical School, Gwangju,

Eski yayınların aksine persiste kandidemi ve nonpersistan hastalar arasında anlamlı mortalite farkı yok

%36 (26/71) vs %26 (27/103) (p <.180)

Kang SJ, J Infection, 2017

TEŞEKKÜRLER