Antifungal Yönetim: Kandida İnfeksiyonları

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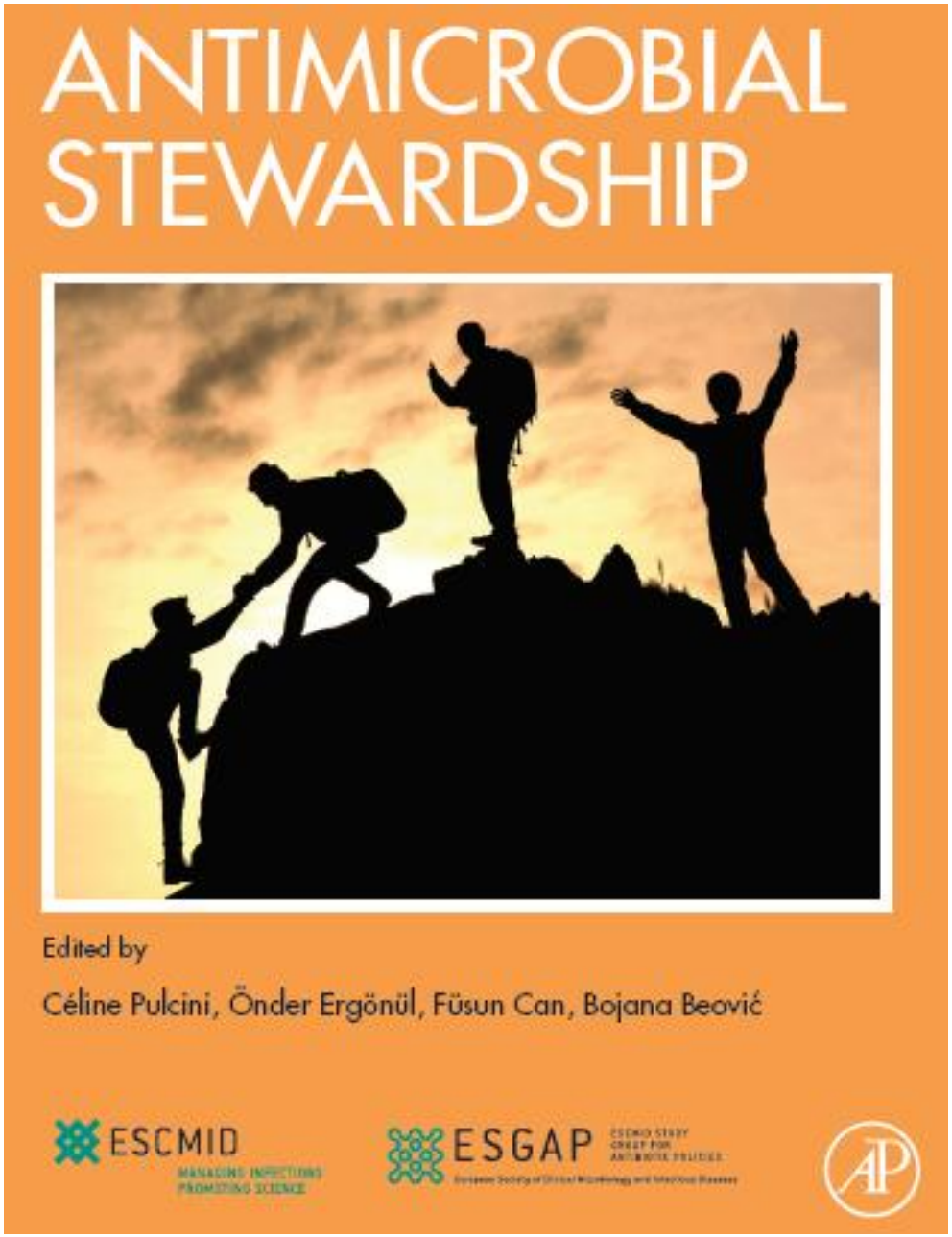
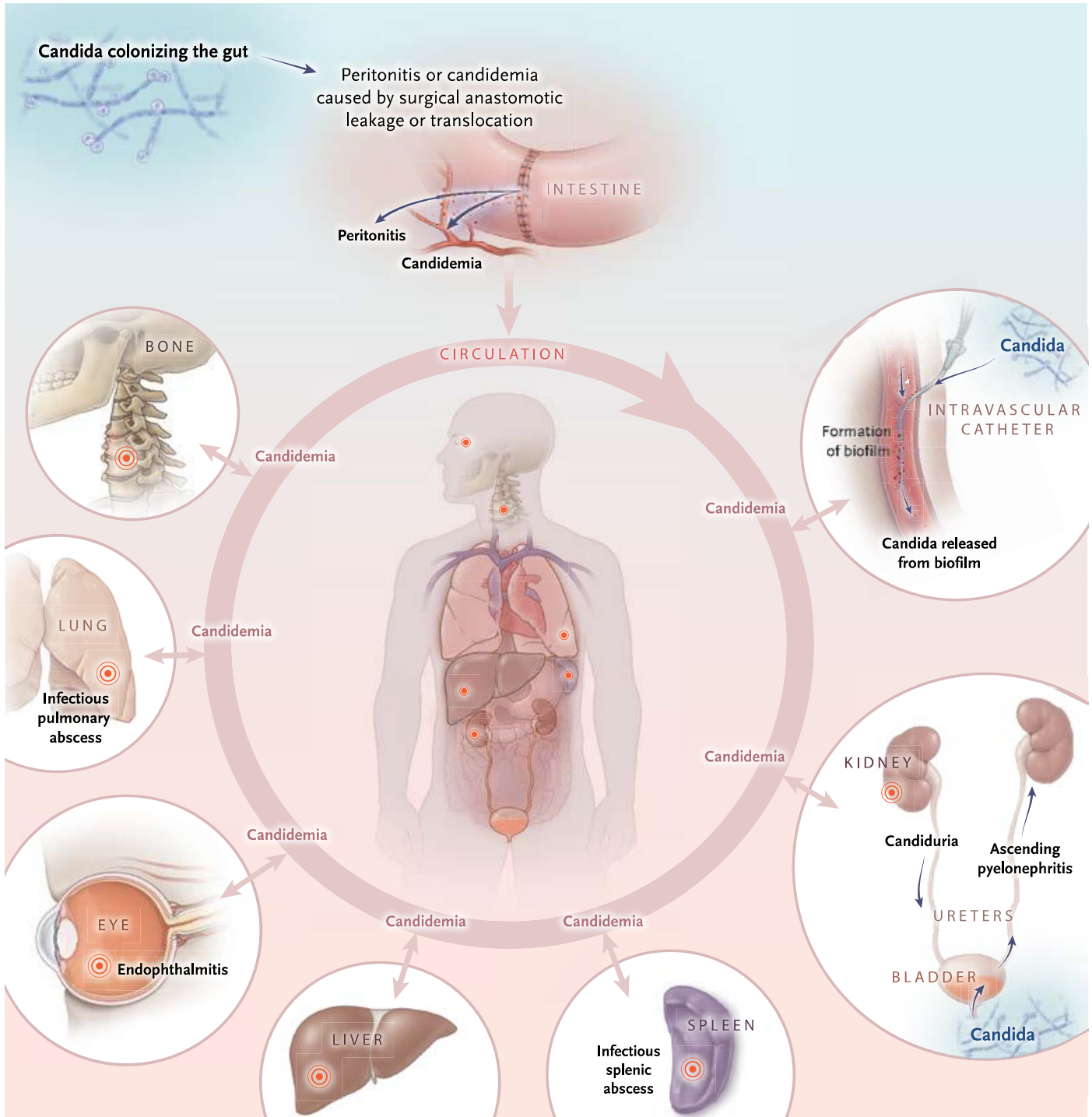
29 Kasım 2017, Antalya



Antifungal Stewardship

Ozlem K. Azap* and Önder Ergönül**
*Başkent University, Ankara, Turkey
**Koç University, Istanbul, Turkey



Invazif Kandidiyaz:

candidemia and deep-seated tissue candidiasis.

Fatalite %40'a kadar çıkabilir.

Kullberg & Arendrup NEJM 2015.

Olgu 1

- 70 yaşında, erkek hasta
- DM
- Whipple operasyonu
- Operasyondan 1 hafta sonra yüksek ateş
- CRP:350, prokalsitonin:8

- ?

TANI :

PANKREAS; PANKREATİKODUODENEKTOMİ:

TÜMÖR:
MİKST ASİNER HÜCRELİ NÖROENDOKRİN KARSİNOM.
ÇAP: 3,7 CM.

TÜMÖR EVRESİ:
pT3 N1 M_ (EVRE İLE İLGİLİ PARAMETRELER AŞAĞIDA DETAYLANDIRILMIŞTIR).

İNVAZYON ALANI:
TÜMÖR SUPERİOR MEZENTERİK VENİ (PİYES ÜZERİNDEKİ BÖLÜMÜNÜ) VE PERİPANKREATİK YUMUŞAK DOKUYU İNVAZE ETMİŞTİR (pT3).

NEKROZ	: VAR, KONFLUEN.
LENFATİK İNVAZYON	: VAR.
VASKÜLER İNVAZYON	: VAR.
PERİNÖRAL İNVAZYON	: VAR.

Kan: E.faecium

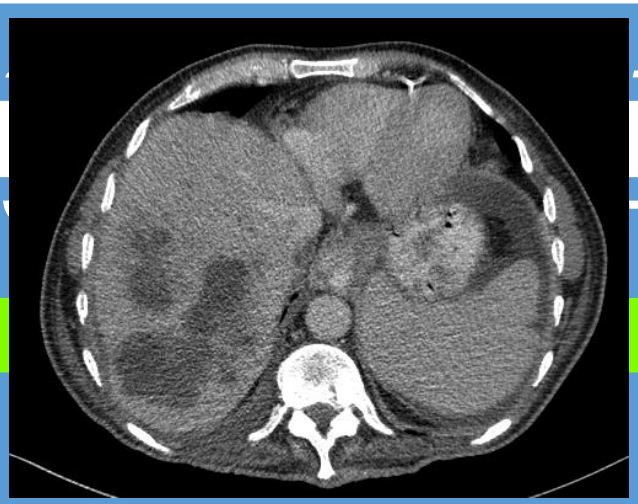
4.YATIŞ

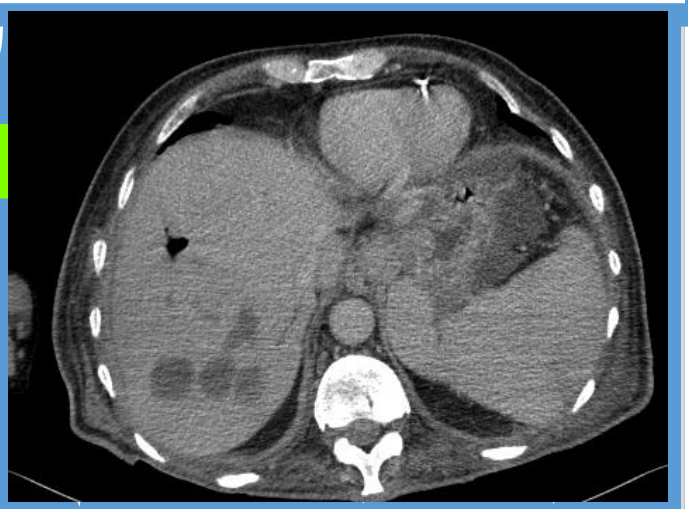
Karaciğer aspirat:
E.Faecium
Stenotrophomonas maltophilia
Candida spp

Kan: MRSE

Kan: E.coli

6. YATIŞ





Candida glabrata MIC değerleri (Karaciğer koleksiyon sıvısı; 2 Mart 2015)

1.	Voriconazole	0.023 micg/mL
2.	Flucanazole	1.5 micg/mL
3.	Posaconazole	0.5 micg/mL
4.	Micafungin	<0.02 micg/mL
5.	Caspofungin	2 micg/mL
6.	Anidulafungin	<0.02 micg/mL
7.	Amphotericin B	4 micg/mL

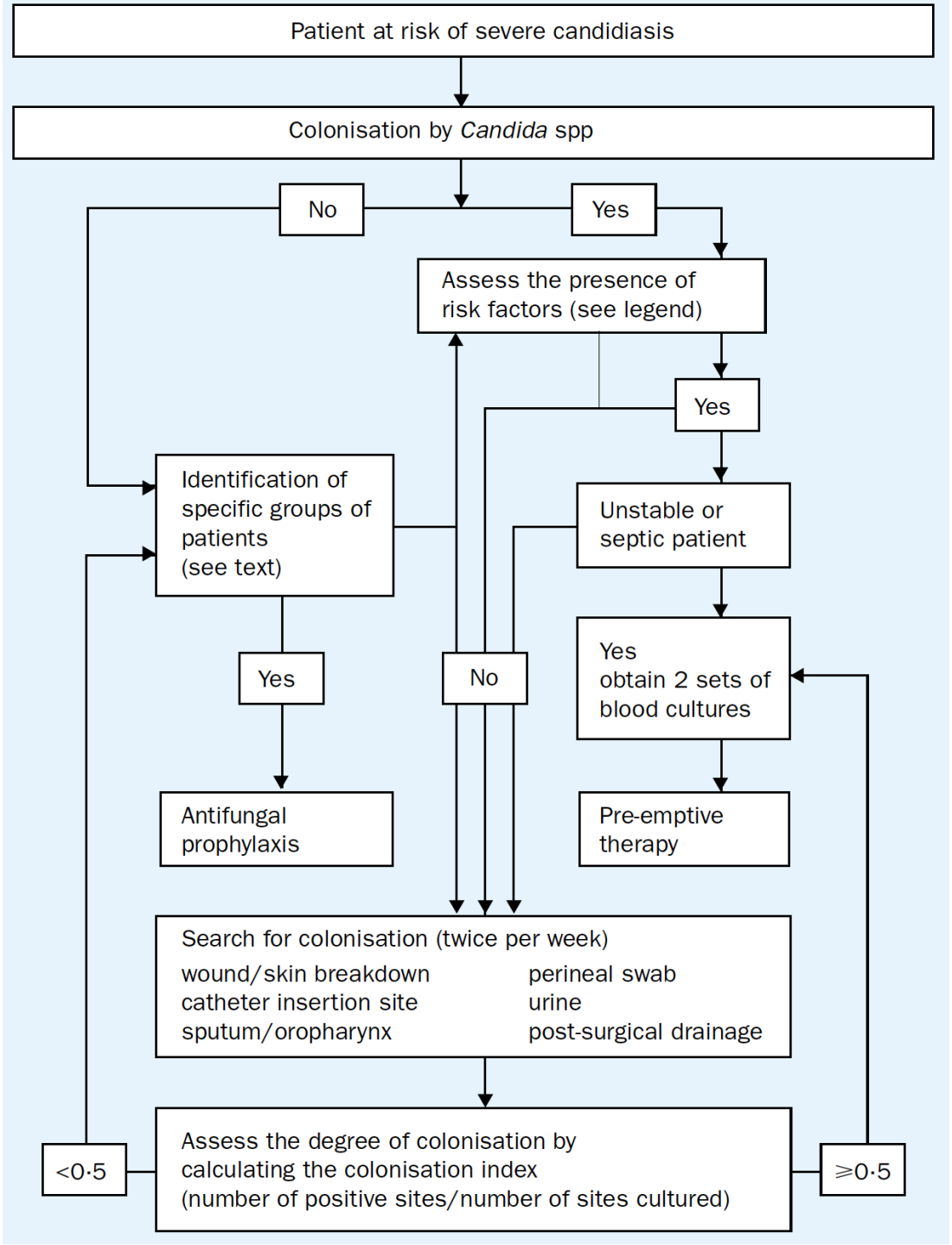
Candida parapsilosis MIC değerleri (Kan kültürü; 9 Mart 2015)

1.	Voriconazole	0.064 micg/mL
2.	Flucanazole	2 micg/mL
3.	Posaconazole	0.094 micg/mL
4.	Micafungin	<0.006 micg/mL
5.	Caspofungin	1.5 micg/mL
6.	Anidulafungin	<0.003 micg/mL
7.	Amphotericin B	0.38 micg/mL
8.	Itraconazole	2 micg/mL

Kronik dissemine kandidiyaz (hepatosplenik kandidiyaz)

Büyük çoğunlukla hematolojik kanser hastalarında görülür.

Çok nadiren, nötropenik olmayan hastalarda görülebilir.



Kandidemi Risk Faktörleri

1. Candida kolonizasyon
2. Antibiyotik kullanımı
3. Iv kateter
4. Idrar sondası
5. Nötropeni
6. Ishal
7. Parenteral beslenme
8. Antasid kullanımı
9. Steroid
10. Kemoterapi
11. Renal yetmezlik
12. Mekanik solunum
13. Uzun yatış
14. Hastalık ciddiyeti
15. Yas

Eggiman, Lancet ID, 20

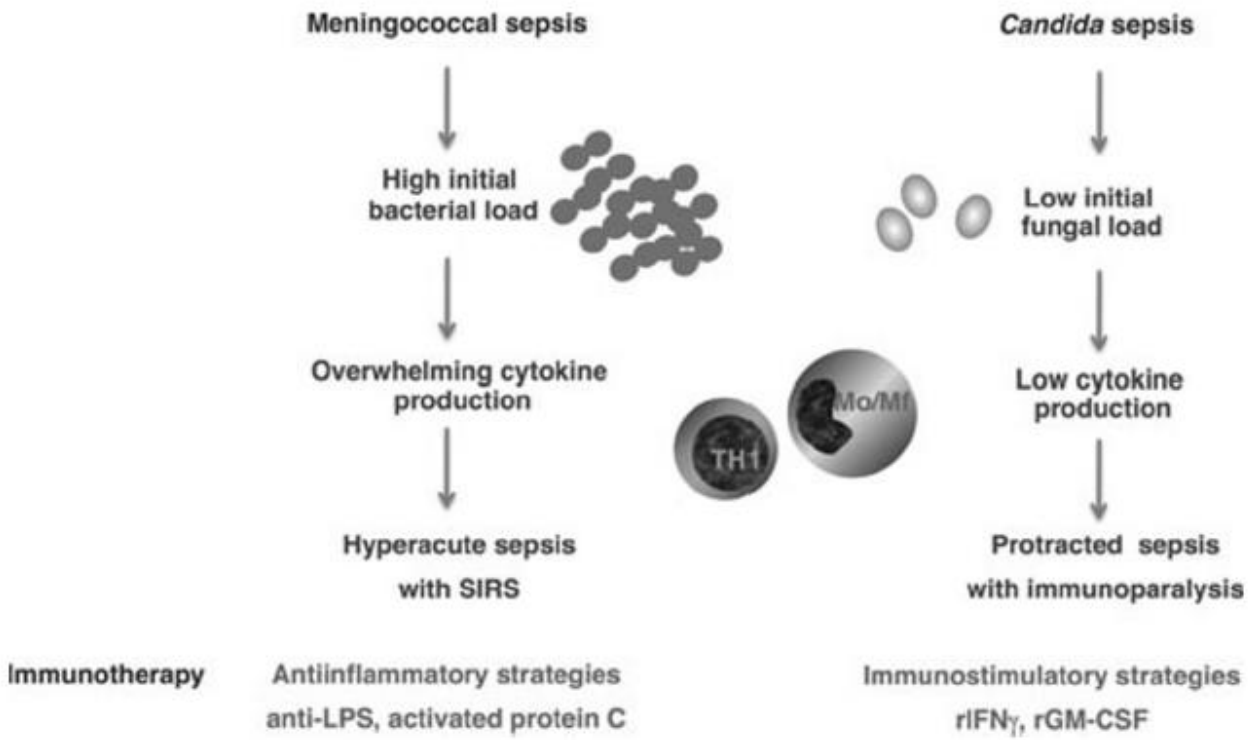


FIG. 2. The role of proinflammatory cytokines during sepsis: whereas proinflammatory cytokines are overwhelmingly released during acute meningococcal sepsis, the concentrations found during systemic candidiasis are much lower. This is partly because of differences in microbial load in the two infections. It is therefore late-stage immunoparalysis, rather than the acute cytokine storm, that is the main immunological disturbance in systemic candidiasis, and the patient would benefit from enhancement of the host defence. LPS, lipopolysaccharide; Mo/Mf, monocyte/macrophage; rGM-CSF, recombinant granulocyte–macrophage colony-stimulating factor; rIFN-γ, recombinant interferon-γ; SIRS, systemic inflammatory response syndrome; Th, T-helper lymphocyte.

PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency

Agata Drewniak,[1,2] Roel P. Gazendam,[1] Anton T. J. Tool,[1] Michel van Houdt,[1] Machiel H. Jansen,[2] John L. van Hamme,[1] Ester M. M. van Leeuwen,[2] Dirk Roos,[1] Emmanuel Scalais,[3] Carine de Beaufort,[4] Hans Janssen,[5] Timo K. van den Berg,[1] and Taco W. Kuijpers[1,6]

[1]Sanquin Research, and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [2]Department of Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands; [3]Division of Pediatric Neurology, Centre Hospitalier de Luxembourg, Luxembourg; [4]Division of Pediatric Endocrinology, Centre Hospitalier de Luxembourg, Luxembourg; [5]Division of Cell Biology, Dutch Cancer Institute, Amsterdam, The Netherlands; and [6]Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Key Points

- Human CARD9 deficiency is characterized by a selective neutrophil killing defect, resulting in invasive candidiasis.

Caspase recruitment domain–containing protein 9 (CARD9) is an adaptor molecule in the cytosol of myeloid cells, required for induction of T-helper cells producing interleukin-17 (Th17 cells) and important in antifungal immunity. In a patient suffering from *Candida dubliniensis* meningoencephalitis, mutations in the *CARD9* gene were found to result in the loss of protein expression. Apart from the reduced numbers of $CD4^+$ Th17 lymphocytes, we identified a lack of monocyte-derived cytokines in response to *Candida* strains. Importantly, CARD9-deficient neutrophils showed a selective *Candida albicans* killing defect with abnormal ultrastructural phagolysosomes and outgrowth of hyphae. The neutrophil killing defect was independent of the generation of reactive oxygen species by the reduced NAD phosphate oxidase system. Taken together, this demonstrates that human CARD9 deficiency results in selective defect in the host defense against invasive fungal infection, caused by an impaired phagocyte killing. (*Blood*. 2013;121(13):2385-2392)

Blood, 2013

Candida spp.: At a Glance

	Features	Antifungal resistance
C. albicans	Responsible for about 50% of Candidemia	Fluconazole 1-2%
C. parapsilosis	Biofilm Skin contamination Fatality is < than *C.albicans* Southern Europe	MIC of echinocandins are high
C. glabrata	Elderly, HIV+ Northern Europe	Dose related resistance for azoles
C. tropicalis	More common among cancer pts	Less R to Fluconazole
C. krusei	Less common Fatality is > *C.albicans*	R to fluconazole Echinocandins considered

Azap O, Ergonul O, AFS, 2017

Yoğun Bakımda İnfeksiyon Etkeninin Saptanma Zamanı

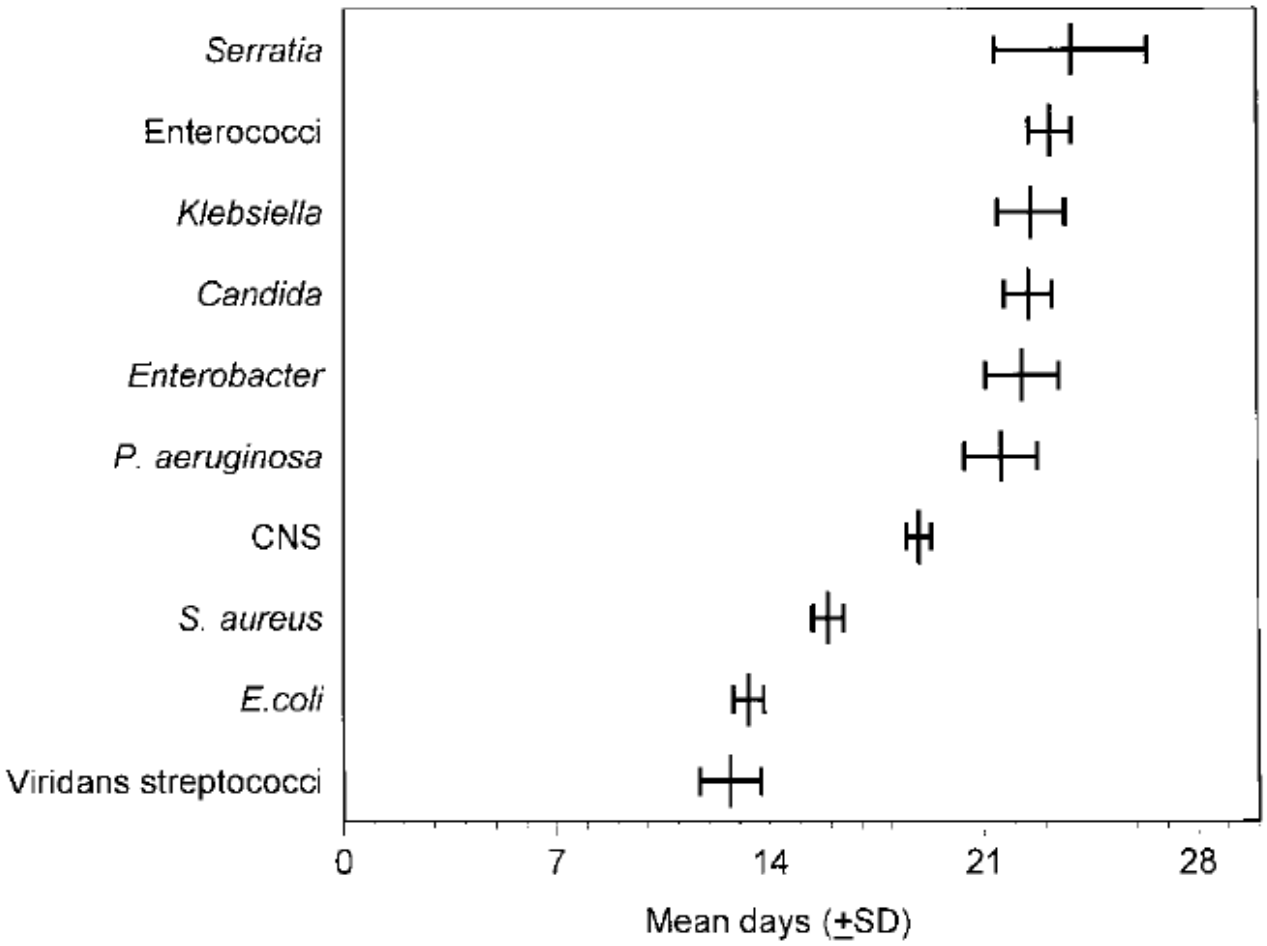


Figure 2. Time from hospital admission to bacteremia by pathogen (mean ± SD) among 49 sentinel hospitals throughout the United States. CNS = coagulase-negative staphylococci; *E. coli* = *Escherichia coli; P. aeruginosa* = *Pseudomonas aeruginosa; S. aureus* = *Staphylococcus aureus.*

Edmond, CID, 199

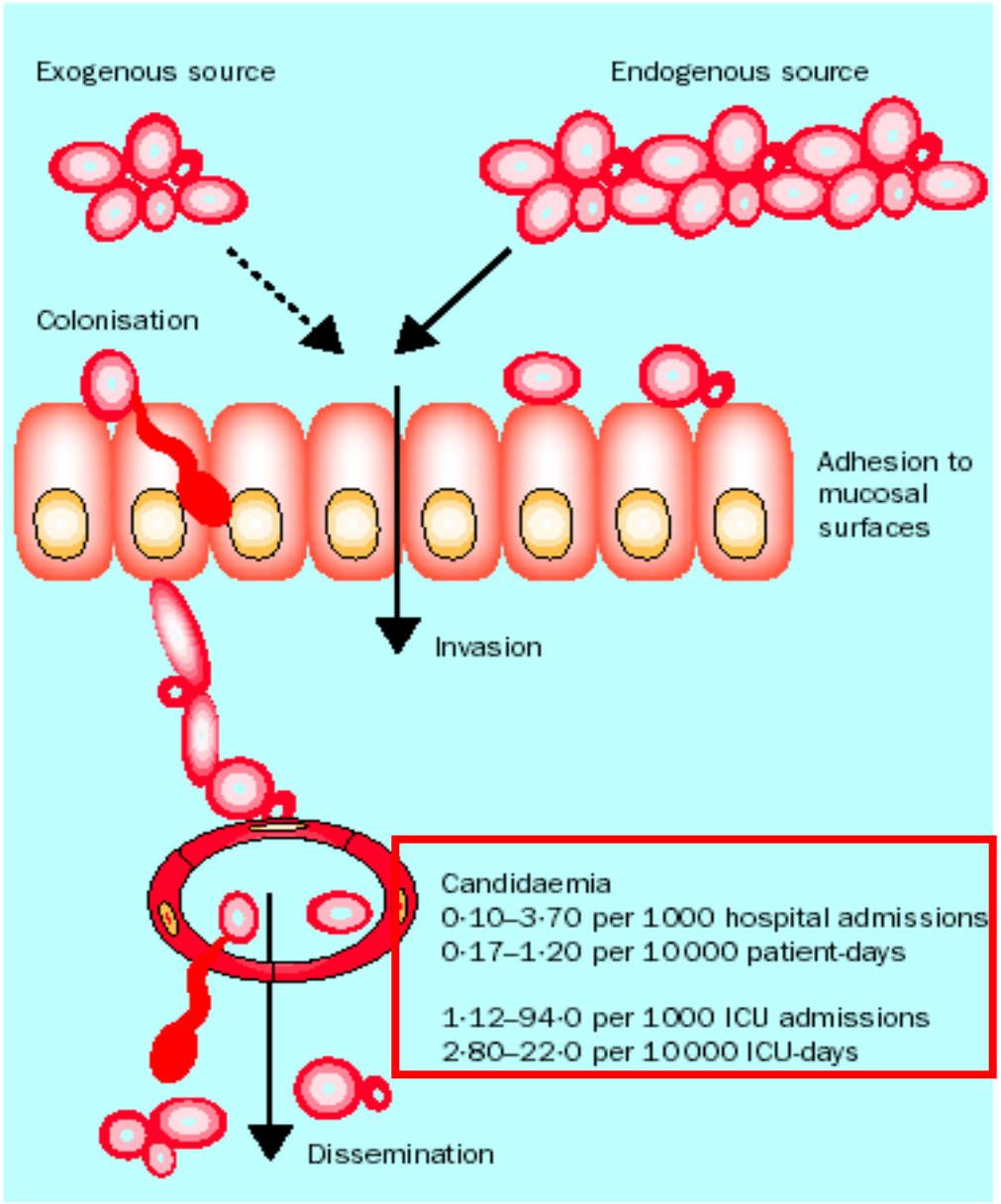
KOLONİZASYON

Endojen (en sık)

1. **GİS**
2. **Cilt**
3. **Mukoza**

Eksojen (nozokomiyal)

1. **Sağlık çalışanı**
2. **Kolonize aletler**



Solunum Örneklerinde Candida

- Oral mukozada kolonizasyon
- Solunum mukozasında kolonizasyon
- Balgam kültürü: tanı değeri çok düşük
- BAL kültüründe kandida üremesi olursa:
  - Nötropenik olmayan hastalarda PPV < %30
  - OTOPSİ ÇALIŞMALARI kolonizasyon lehine

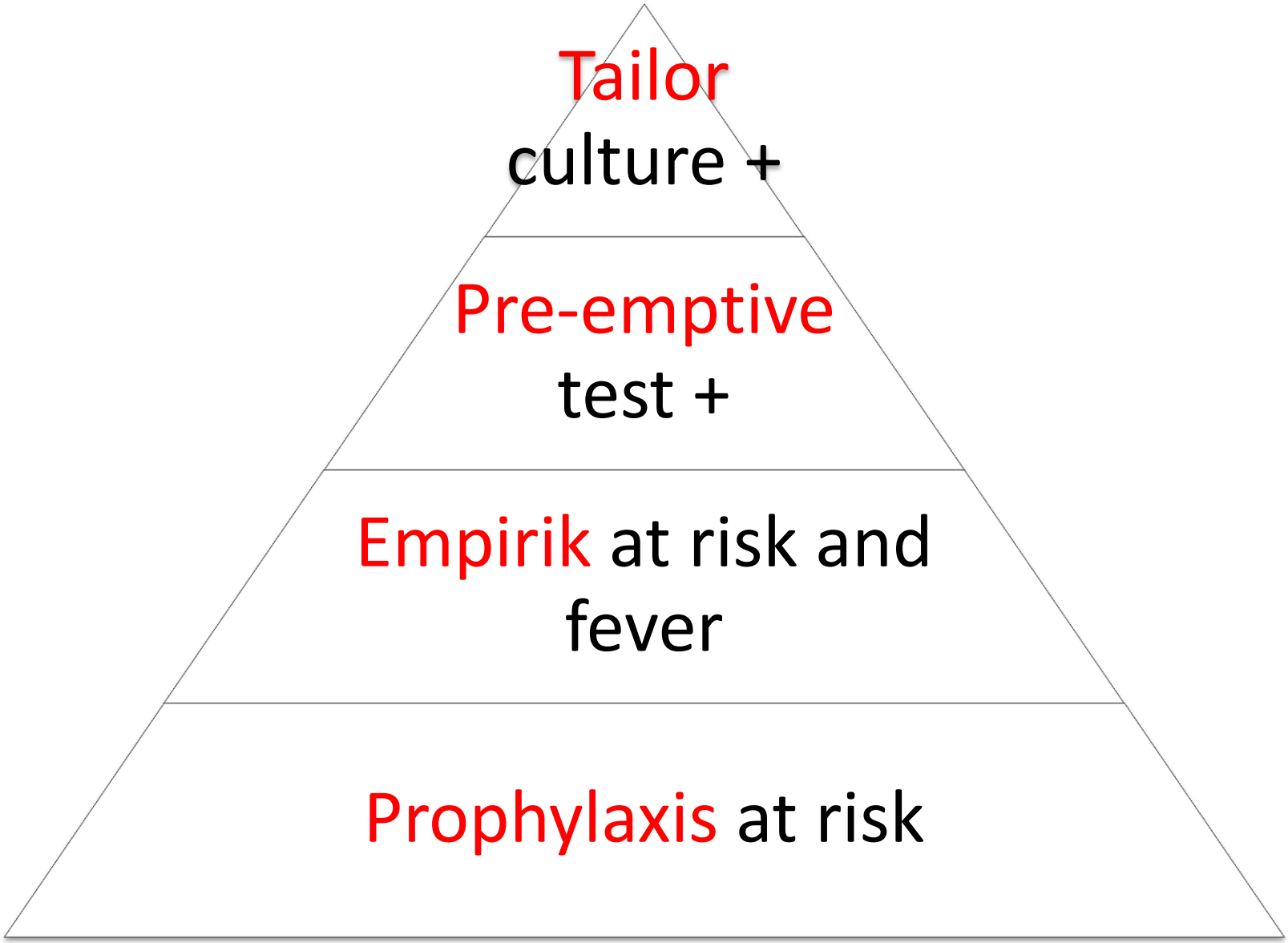
Azoulay et al, Intensive Care Med (2004) 30:1384–1389

Kateter İnfeksiyonu

- 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

Tanı


Tailor
culture +
Pre-emptive
test +
Empirik at risk and
fever
Prophylaxis at risk

Diagnosis

- **Blood Culture**
  - Only diagnostic approach that allows subsequent susceptibility testing.
  - Blood culture sensitivity: 21-71% reported in autopsy studies.
  - Blood cultures: slow turn-around times and revealed late .
  - Positive blood cultures should prompt the immediate initiation of therapy and a search for metastatic foci.
- **β-d-glucan**
  - Could be false positive.
  - The major benefit is negative predictive value.
- **Mannan/Anti-mannan**
  - Maybe in hepatosplenic candidiasis
- **PCR**
  - not well standardized yet

Differences in Stewardship

Antibiotic

- Diagnosis
  - CRP
  - Procalcitonin
  - Culture: earlier
- Resistance reports
  - Set
- Switch
- Consensus in treatment better

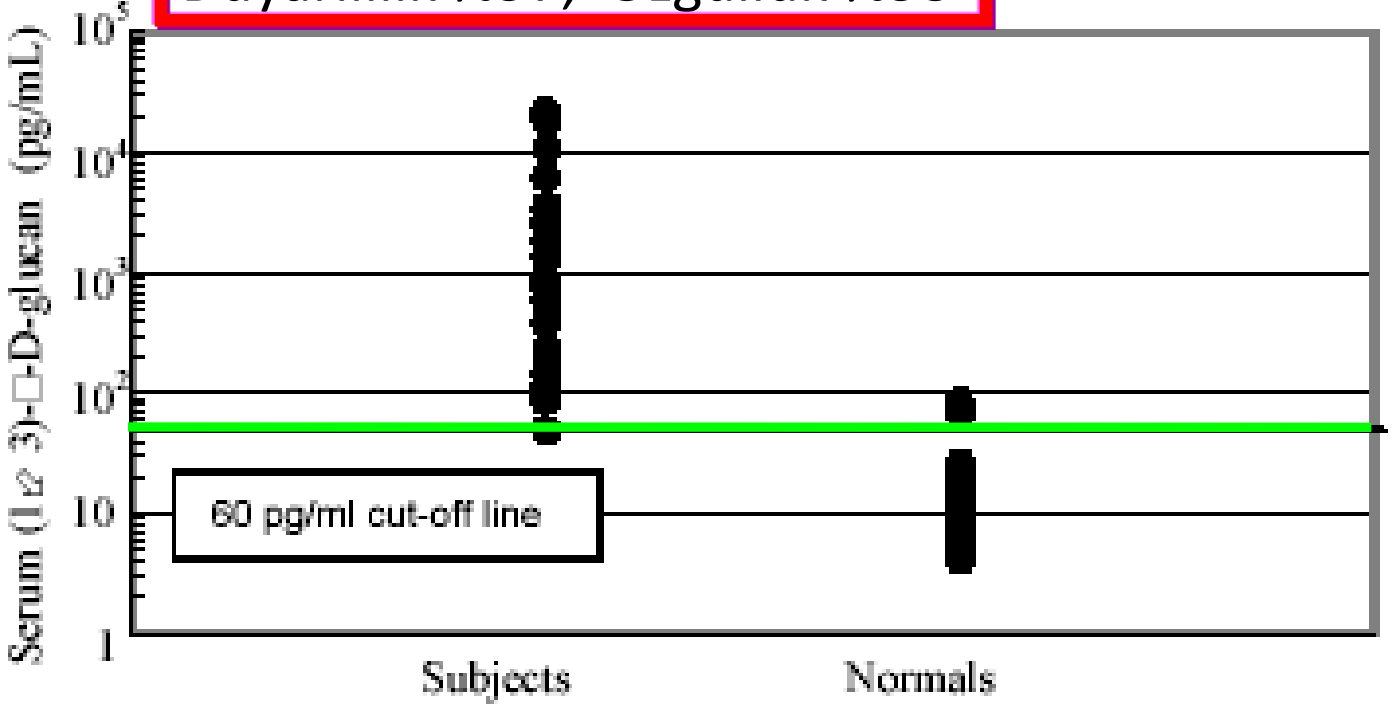
Antifungal

- Diagnosis
  - BDG
  - GM/CT
  - Culture: not very early
    - Difficult if seated deeply
- Resistance reports
  - Improving
- Switch: not well developed
- Consensus in treatments needs to be improved

Beta Glukan Testi

Kandidemik 30 hastada B glukan testi

Duyarlılılk %97, Özgüllük %93



Kandidalara Özgü Değil: Panfungal

Odabasi Z, Clin Infect Dis 2004

Mannan + Anti Mannan

- On dört çalışmaya dayanan bir meta-analiz
- Kültür pozitifliğinden ortalama Mn: 6, Anti-mn 7 gün önce +

	Duyarlılık (%)	Özgüllük (%)
Mannan	**58**	**93**
Anti Mannan	**59**	**83**
Mannan + Anti Mannan	**83**	**86**

Mikulska M, Critical Care 2010

İnvaziv Kandidiyaz Kesin Tanı

- Kan kültürü pozitifliği

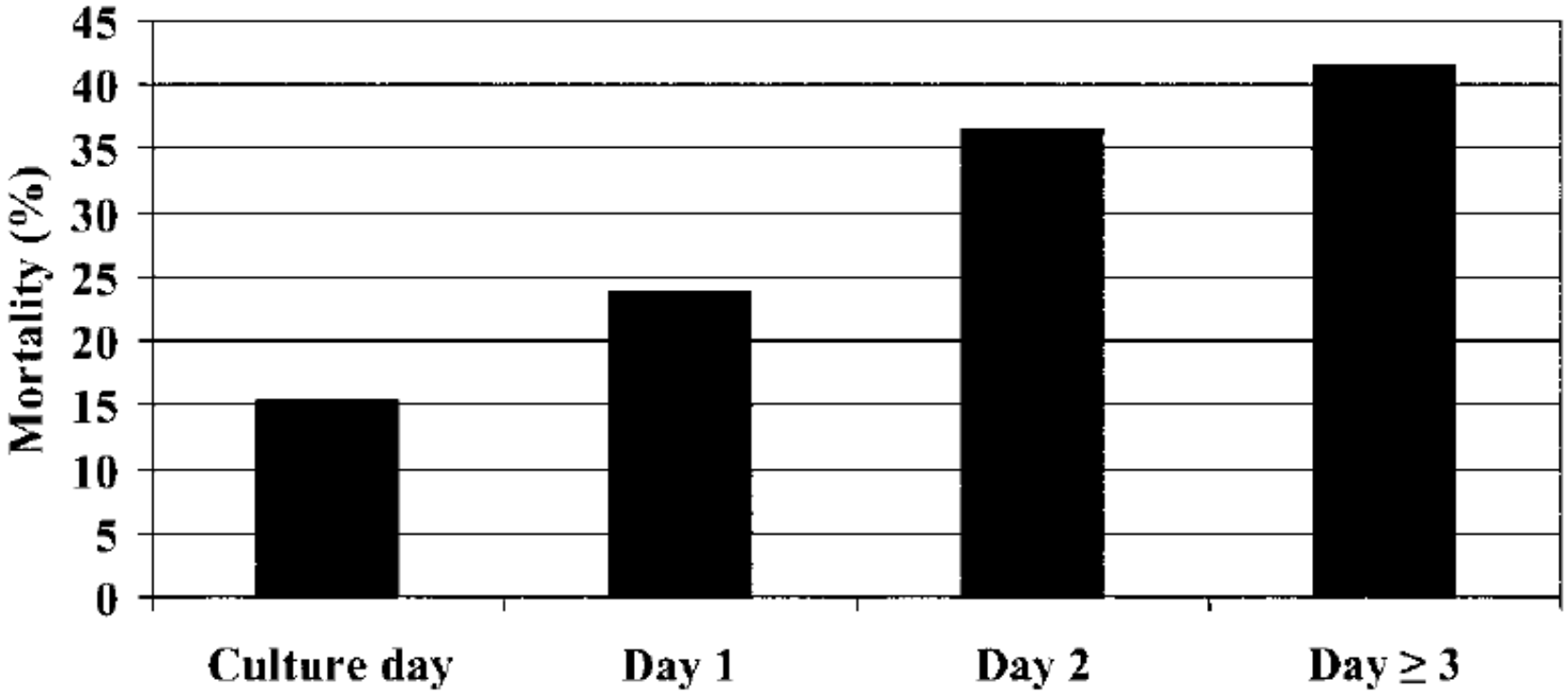
veya

- Steril vücut sıvısı ya da dokuda üretilmesi (idrar ve sinüs aspiratı hariç)

veya

- Histolojik tanı

Tedavi Zamanlaması ve Mortalite



Antifungal Başlama Günü

Garey KW et al. CID 2006; 43:25-31.

Skorlama

Leon et al, Kandida Skoru

- >7 gün yatan 1699 ICU vakasında prospektif kohort
  - Cerrahi
  - Multifokal kolonizasyon
  - TPN
  - Ağır sepsis
- ≥ 2.5 skor ile %81 duyarlılık, %74 özgüllük
- Başka bir çalışmada skorun < 3 olması ile NPV %98
- Kandida skoru, kolonizasyon indeksinden üstün bulundu

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization*

Cristóbal León, MD; Sergio Ruiz-Santana, MD, PhD; Pedro Saavedra, PhD; Benito Almirante, MD, PhD; Juan Nolla-Salas, MD, PhD; Francisco Álvarez-Lerma, MD, PhD; José Garnacho-Montero, MD; María Ángeles León, MD, PhD; EPCAN Study Group

İnvazif Kandidiyaz ciddi sepsis ve septik şoka benzer bir tablo.

Yeni antifungallere rağmen geç saptanırsa fatalite %40. (Ostrosky-Zeihcner, CCM, 2006)

Acaba invazif Kandida infeksiyonu önceden tahmin edilebilir mi?

Bu amaçla Kandida skoru oluşturulabilir mi?

León, et al. Crit Care Med, 200

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000

Candida score = .908 × (total parenteral nutrition) + .997 × (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 × (total parenteral nutrition) + 1 × (surgery) + 1 (multifocal *Candida* species colonization) + 2 × (severe sepsis). All variables coded as follows: absent, 0; present, 1.

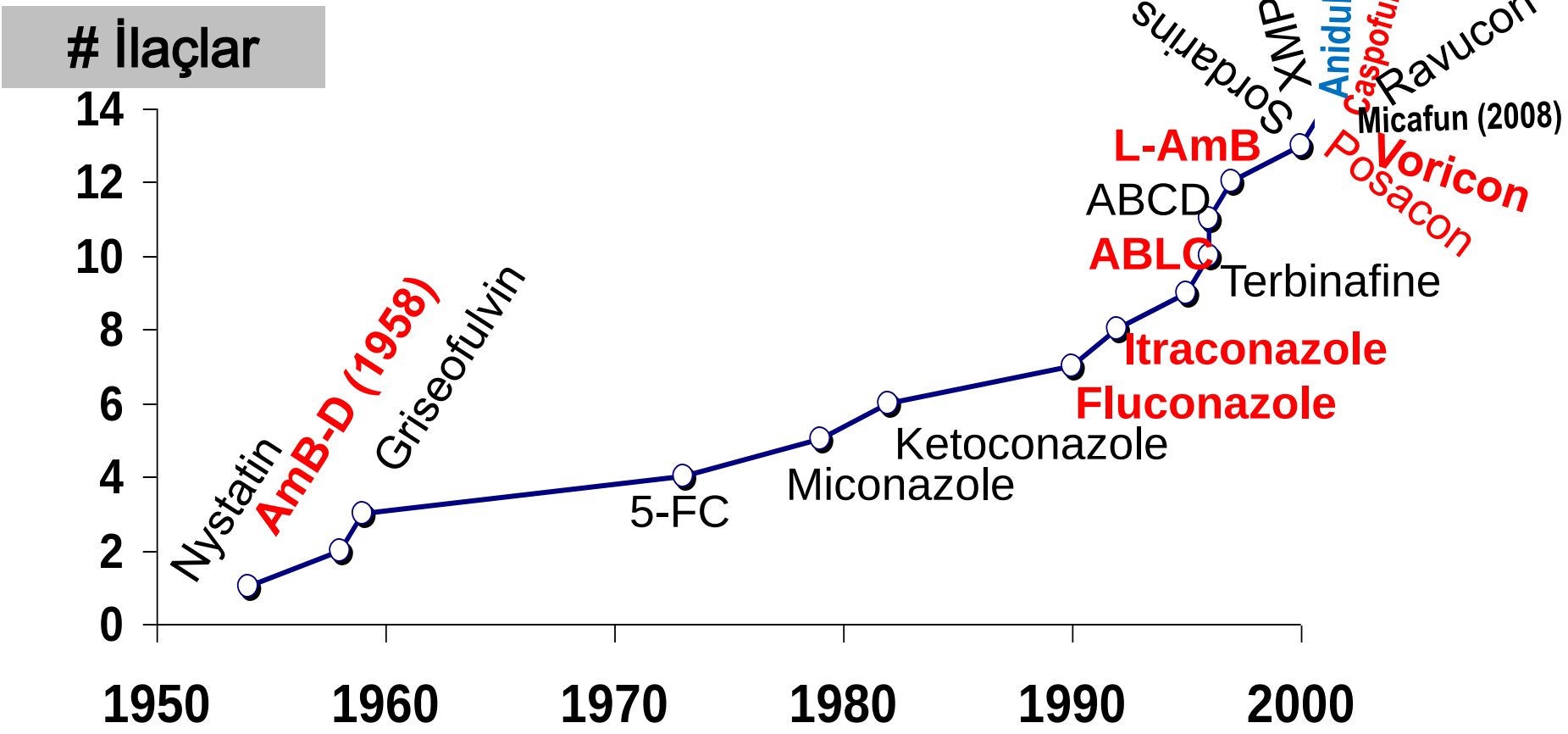
Leon, et al. Crit Care Med, 200

Paphitou et al, Kandida skoru

- Cerrahi YBÜ, 327 vaka, kohort
- >3 gün yatan ve aşağıdakilerden bir tanesi
  - DM + Diyaliz + TPN + Geniş spektrum antibiyotik alanlarda %17 kandidiyaz gelişirken
  - Bunların olmadığı hastalarda %5 ($p < 0.01$)
- Vakaların %52 ‘si bu skora uyuyordu
- Kandidiyazların %78 ‘ini yakaladı

Tedavi

Tıbbi mikoloji: Son 60 yılı



IFI'de kullanılan antifungal ilaçların sınıflaması: 4 sınıf

1- Polienler

- AmB deoksikolat
- Lipid-bazlı AmB formülasyonları
  - Lipozomal AmB (L-AmB)
  - AmB lipid kompleksi (ABLC)
  - AmB kolloidal dispersiyon (ABCD)

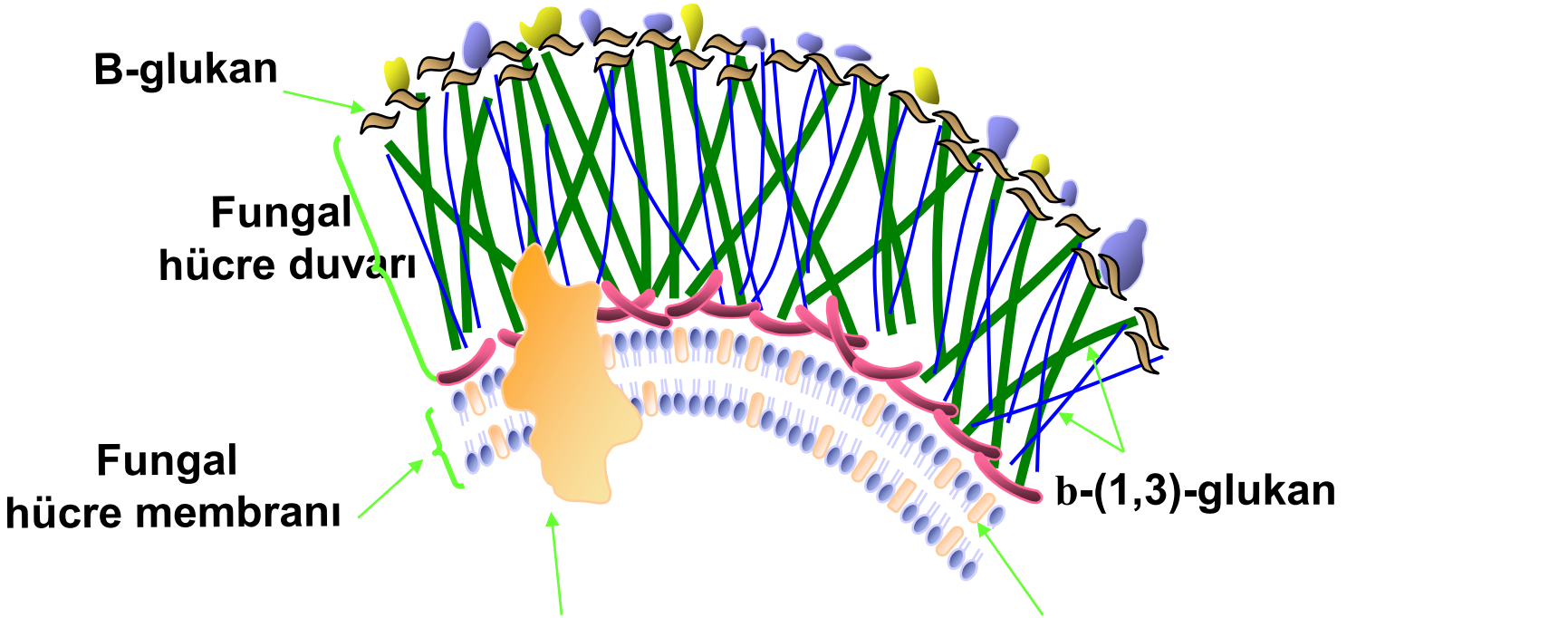
2- Triazoller → Flukonazol, itrakonazol, vorikonazol, posakonazol

3- Ekinokandinler → Kaspofungin, anidulafungin, mikafungin

4- Pirimidin analoğu → 5-flurositozin (5FC / flusitozin)

Antifungallerin mantarda etki yerlerine göre sınıflaması

1- Mantar duvar sentezini bozanlar→ Ekinokandinler
2- Mantar sitoplazmik membranını bozanlar→ Polienler / Triazoller
3- Mantar DNA sentezini bozanlar→ Pirimidin analoğu



Ekinokandinlerle azoller arasında çapraz direnç oluşmaz

Antifungaller ve immünosuppresörlerin klinik etkileşimleri

	Siklosporin A	Takrolimus	Mikofenolat mofetil	Sirolimus
Lipozomal AmB[1]	Potansiyel nefrotoksisite	Potansiyel nefrotoksisite	NR	NR
Flukonazol[2]	Siklo AUC ↑ (1.8 kat)	Oral takro kons ↑ (5 katta kadar)	NR	Sirol kons ↑
İtrakonazol[3]	Siklo ↑	Takro ↑	NR	Sirol kons ↑
Vorikonazol[4]	Siklo C_{max} & AUC ↑ (%13, %70)	Takro C_{max} & AUC ↑ (%117, % 221)	NR	Sirol C_{max} & AUC ↑ (6.6 kat, 11 kat)
Posakonazol[5]	Siklo kons↑	Takro C_{max} & AUC ↑ (%121, % 358)	NR	Sirol C_{max} & AUC ↑ (6.7-kat, 8.9-kat)
Kaspofungin[6]	Kaspofungin AUC ↑ (%35)	Takrolimus C_{min} ↓ (% 26)	–	NR
Mikafungin[7]	–	–	–	Sirol AUC ↑ (%21)
Anidulafungin[8]	–	–	NR	NR

NR — KUB'de spesifik öneri yok

Doz ayarlaması gerekmez

Eş zamanlı kullanılabilir , ancak monitorizasyon/doz ayarlaması gerekir

Kontra-endikedir

1. AmBisome® (amfoterisin B) Kısa Ürün Bilgisi. Gilead Sciences. August 2012; **2.** TRIFLUCAN® (flukonazol) Kısa Ürün Bilgisi. Pfizer Ltd. Ekim 2009
3. Sporanox® (itrakonazol) Kısa Ürün Bilgisi .Janssen.Haziran 2014; **4.** Vfend® (vorikonazol) Kısa Ürün Bilgisi. Pfizer Ltd. Ocak 2014
5. Noxafil® (posakonazol) Kısa Ürün Bilgisi. Merck Sharp & Dohme. Şubat 2014; **6.** Cancidas® (kaspofungin) Kısa Ürün Bilgisi. Merck Sharp & Dohme. Ağustos 2014
7. MYCAMINE™ (mikafungin sodyum) Flakon Kısa Ürün Bilgisi. Astellas Pharma İlaç Tiç.A.Ş. Ocak –Şubat 2014 **8.** Eraxis® (anidulafungin) Kısa Ürün Bilgisi. Pfizer Ltd. Temmuz 2014

Rehberler

Rehberler Tartışması Ne Durumda?

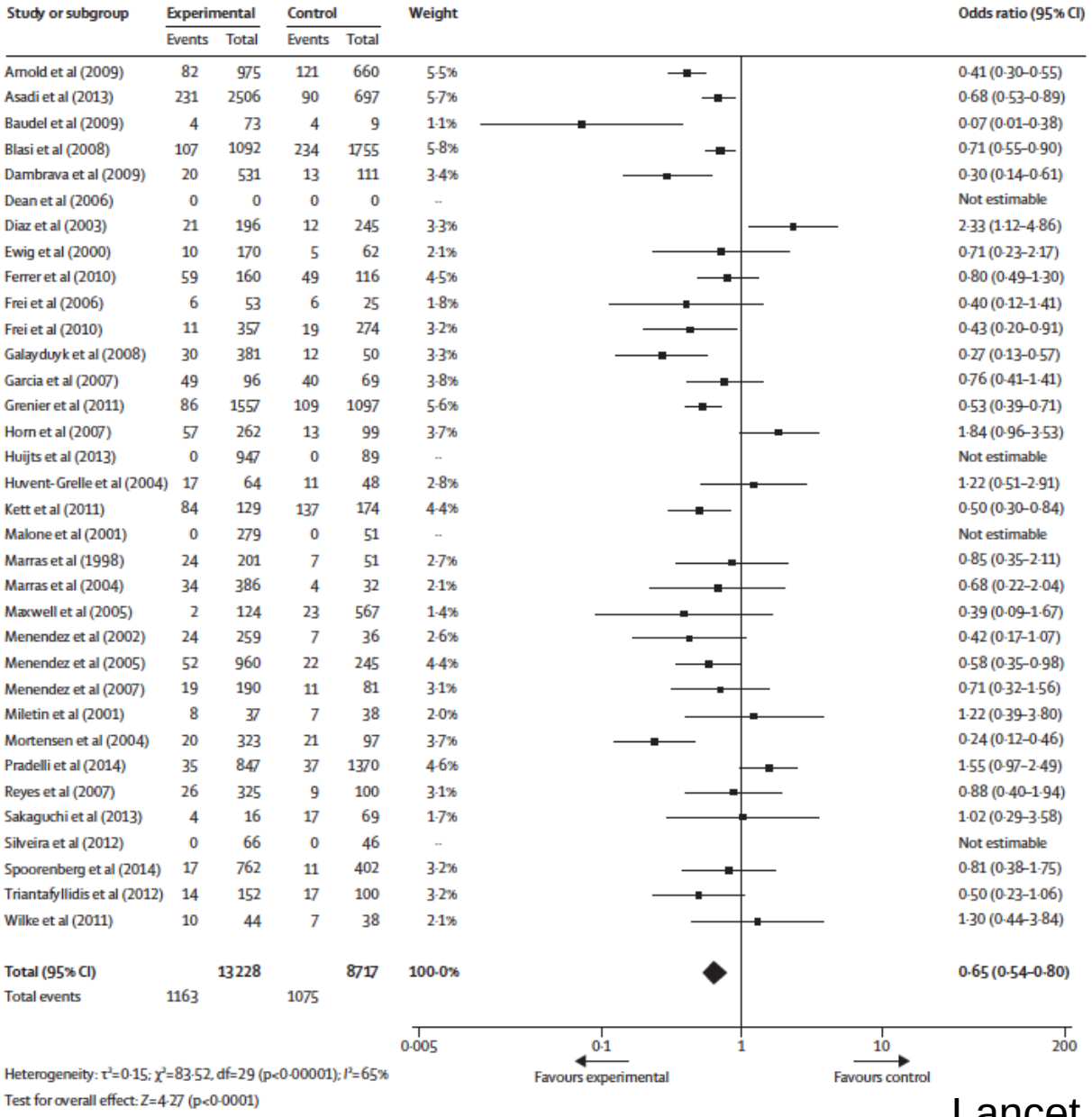
Rehberler

- Fabrikasyon
- Yayınlanmış veriler
  - RKÇ
  - Yayınlanma yanlılığı
  - Pek çok hata/yanlılık
- Endüstrinin etkisi
- Gelişmiş ülkeler odaklı

Rehber karşıtlığı

- Haute cotur, butik yaklaşım
- Pratik
  - Kendinden menkul
  - ”Deneyimlerime göre”
  - “En büyük benim”
- Tümden bağımsız mı?
- Yerel veriler yok

Rehberlere Uyumun Mortaliteye Etkisi



Lancet Infect Dis 2016

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

by Frederic Tissot, Samir Agrawal, Livio Pagano, Georgios Petrikkos, Andreas H. Groll, Anna Skiada, Cornelia Lass-Flörl, Thierry Calandra, Claudio Viscoli, and Raoul Herbrecht

Table 4: ECIL-6 recommendations for initial first-line treatment of candidemia

	Overall population	Hematological patients
Antifungal therapy		
- Micafungin [a]	A I	A II
- Anidulafungin	A I	A II [b]
- Caspofungin	A I	A II
- Liposomal amphotericin B	A I	A II
- Amphotericin B lipid complex	B II	B II
- Amphotericin B colloidal dispersion	B II	B II
- Amphotericin B deoxycholate [c]	C I	C II
- Fluconazole [d,e]	A I	C III
- Voriconazole [d]	A I	B II
Catheter removal [f]	A II	B II

[a] See warning box in European label; [b] Provisional grading; [c] Close monitoring for adverse event is required ; [d] Not in severely ill unstable patients; [e] Not in patients with previous azole exposure; [f] if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended.

Table 5: ECIL-6 recommendations for first-line treatment of candidemia after species identification

Candida species	Overall population		Hematological patients	
C. albicans	Echinocandins [a]	A I	Echinocandins	A II
	Fluconazole [b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins [a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins [a]	A II	Echinocandins [a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins [c]	B II	Echinocandins	B III

[a] same grading for anidulafungin, caspofungin, micafungin ; [b] not in severely ill patients; [c] if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72h), continuing use of echinocandin might be considered

Table 7: ECIL-6 recommendations for first-line treatment of invasive aspergillosis

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (Initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

2016

Antimikrobiyal Yönetimi için Rehberler Yılı

1. ABD: 4 güçlü toplam 28 Öneri
2. Hollanda
3. Almanya

Klinik tablolara özgü algoritmalar

IV. Should ASPs Implement Interventions to Improve Antibiotic Use and Clinical Outcomes That Target Patients With Specific Infectious Diseases Syndromes?

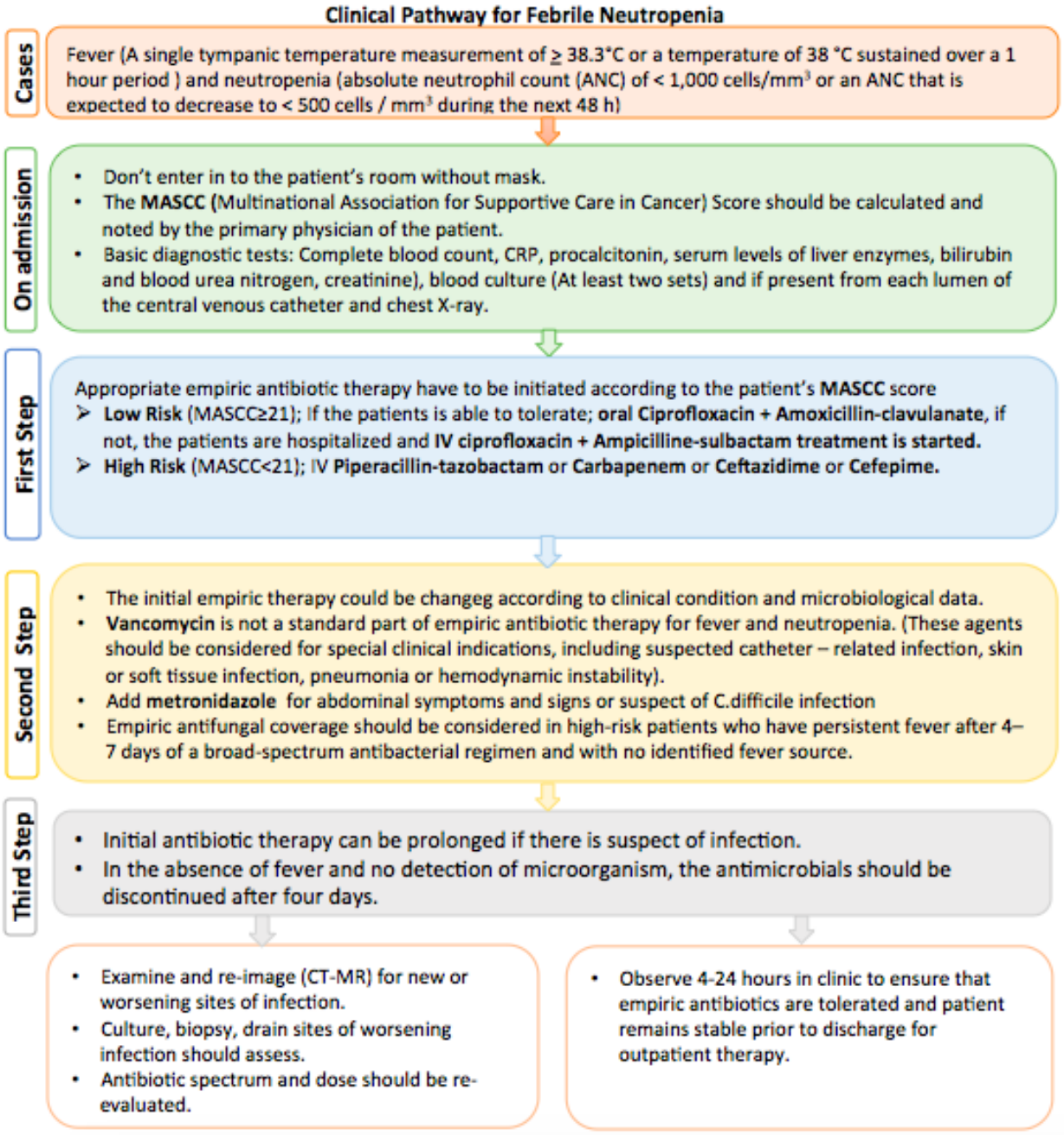
Recommendation

4. We suggest ASPs implement interventions to improve antibiotic use and clinical outcomes that target patients with specific infectious diseases syndromes *(weak recommendation, low-quality evidence)*.

Örnekler

- Febril Nötropeni
- Solunum Yolu İnfeksiyonları
- Akut gastroenteritler
- İdrar yolu infeksiyonları

IDSA 2016



Madran B, Keske Ş, Tokca G, Ferhanoğlu B, Cetiner M, Mandel NM, Ergonul O. Implementation of Antimicrobial Stewardship Program for the Patients with Febrile Neutropenia. Am J Infect Control 2017 (accepted)

IDSA GUIDELINE

Infectious Diseases Society of America hiv medicine association OXFORD

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]

Farklı Ne Var?

- Başlangıçta ekinokandinlerin artan rolü
- Duyarlılık testlerinin önemi
- Değiştirme: Ekinokandinlerden flukonazole geçiş ne zaman?
- Vurgular
  - Risk faktörleri
  - Fundoskopik muayene
  - Kateterin çıkarılması
  - Tedavi süresi

IDSA 2016: Nötropenik olmayan hastalar

- Başlangıç tedavisi ekinokandin
  - Durumu kritik olmayan hastalarda, direnç düşnülmüyorsa alternatif olarak flukonazol

- Azol ve ekinokandin duyarlılık testi:
  - Daha önce ekinokanding tedavisi alanlar
  - *C glabrata* veya *C parapsilosis* infeksiyonları

- Klinik durum stabilleşirse ve flukonazole duyarlıysa ekinokandinden flukonazole geçiş: 5-7 gün

- *C glabrata* infeksiyonunda, yüksek doz flukonazol 800 mg (12 mg/kg) veya voriconazol 200 to 300 (3-4 mg/kg) günde 2 kez düşünülebilir.

IDSA 2016: Nötropenik hastalar

- Başlangıç tedavisi ekinokandin
  - Daha düşük alternatif: amfoterisin B (lipid)
  - Durumu kritik olmayanlarda flukonazol: daha önce flukonazol maruziyeti yoksa.

- *C krusei:* ekinokandin, amfoterisin B (lipid), veya voriconazole

- Metastatik komplikasyonlarda: minimum tedavi süresi eradikasyonu dökümente ettikten sonra 2 hafta

- Funduskopik muayene: nötropeniden çıktıktan 1 hafta sonra

- Kateter çıkarımı olguya özgü değerlendirilmelidir.

Candidemia: Catheter removal

- Removal of central venous line
  - In non-hematological patients **A II**
  - In hematology patients ~~**B III**~~ **B II**
  - ~~Removal is always recommended when *C parapsilosis* is isolated **A II**~~
- When catheter cannot be removed, treatment with an echinocandin or a lipid formulation of amphotericin B is preferred **B III**

Ann Hematol (2016) 95:1435–1455
DOI 10.1007/s00277-016-2711-1

ORIGINAL ARTICLE

Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016

Andrew J. Ullmann[1] · Martin Schmidt-Hieber[2] · Hartmut Bertz[3] · Werner J. Heinz[1] · Michael Kiehl[4] · William Krüger[5] · Sabine Mousset[6] · Stefan Neuburger[7] · Silke Neumann[8] · Olaf Penack[9] · Gerda Silling[10] · Jörg Janne Vehreschild[11] · Hermann Einsele[1] · Georg Maschmeyer[12] · on behalf of the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the DAG-KBT (German Working Group for Blood and Marrow Transplantation)

Table 2 Antifungal prophylaxis

Intention	Intervention	SoR	QoE	Comments
Prevent mould infection in patients without GvHD, day 1–100	Voriconazole 200 mg bid oral or iv[b]	C	I	No difference seen in the trial in comparison to fluconazole
	Posaconazole (suspension) 200 mg tid[b]	B	II_t	Improved overall survival in AML/MDS induction during neutropenia, new formulations (tablet and iv, 300 mg qid) provide a better bioavailability
	Micafungin 50 mg/day	C	I	Only during neutropenia, morbidity advantage
	Itraconazole suspension 2.5–7.5 mg/kg or capsules	C	I	Administered up to 180 days if GVHD was diagnosed; higher toxicity in comparison to fluconazole, TDM: cutoff at 500 mg/mL (AII)
Prevent invasive *Candida* disease in patients without GvHD, day 1–100	Fluconazole 400 mg/day	A	I	Improved survival, note rising incidence of resistant *Candida* species since studies were published
	Voriconazole 200 mg bid oral or iv[b]	B	II_t	Also active against moulds, but no difference seen in the trial between voriconazole and fluconazole
	Posaconazole (suspension) 200 mg tid[b]	B	II_t	Also effective against moulds, new formulations (tablet and iv, 300 mg qd) provide a better bioavailability
	Micafungin 50 mg/day	B	II_t	Also effective against moulds, only during neutropenia, morbidity advantage
	Itraconazole suspension 2.5–7.5 mg/kg or capsules[b]	C	I	See above
Prevent invasive Aspergillosis during GvHD	Posaconazole (suspension) 200 mg tid[b]	A	I	improved survival (lower attributable mortality), new formulations (tablet and iv, 300 mg qd) provide a better bioavailability
Prevent fungal disease relapse (previous IFD)	Voriconazole[b]	B	II	considered as secondary antifungal prophylaxis, dosages as above
	Caspofungin, posaconazole	B	III	
Prevent fungal diseases[a]	Amphotericin B deoxycholate	D	II	Inacceptable toxicity

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Journal of Antimicrobial Chemotherapy

Comparison of the antifungal activity of micafungin and amphotericin B against *Candida tropicalis* biofilms

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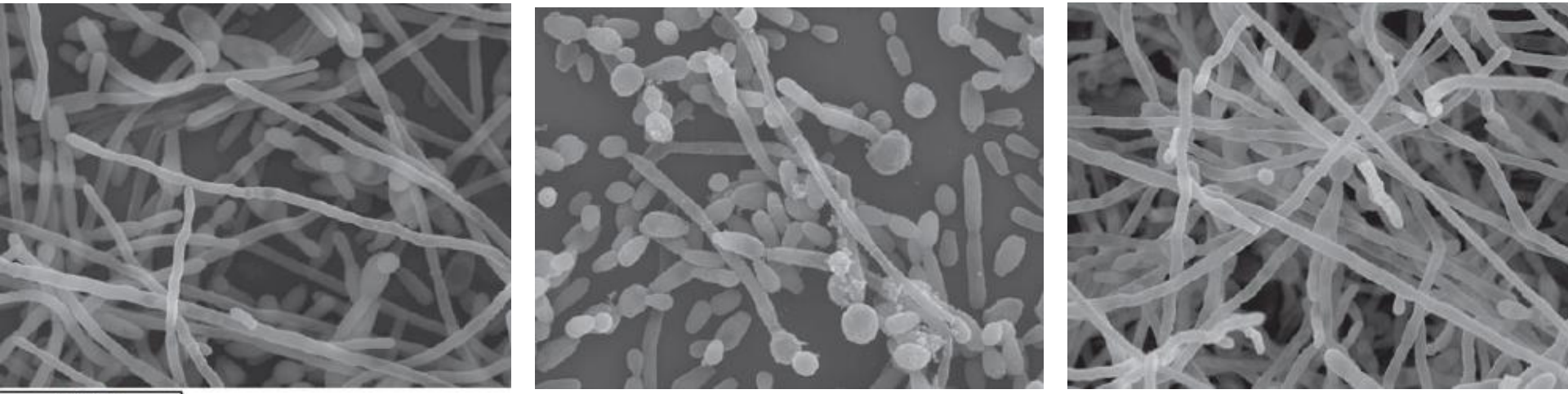
Untreated control

Micafungin

Amphotericin B



Sonuçlar

- Yerel veriler
  - ÇİD Gram Negatif bakteriler
- Yerel uygulamalar
  - Biyobelirteçler
  - Moleküler yöntemler
- Ulusal rehberler
  - Nasıl ilerlemeli?