

# YOĐUN BAKIMDA FUNGAL ENFEKSİYONLAR

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- FUNGAL ENFEKSİYON
  - Artmış mortalite
  - Artmış morbidite
  - YB kalış süresinde artış
  - Hastane kalış süresinde artış
  - Maliyette artış

- İlaç dirençli, mikroorganizmalar (A. Boumani, Pseudomonas) ve fungal enfeksiyonlar ile mortalite artar

# İnvazif Fungal Enfeksiyonlarda Mikrobiyolojik Tanı – Çok Zor

- *Candida* spp sık kolonizasyon etkeni,
- Non steril örneklerden fungal üreme enfeksiyonu göstermez
- Hızlı üreyen bakteri varlığında funguslar baskılanır
- Antifungaller ile profilaksi ve empirik tedaviler

# Fırsatçı Mikoz gelişiminde Rol Oynayan Faktörler

Mukozal ve cilt bariyer bozulması

Candida Spp.  
Aspergillus Spp.

Nötrofil disfonksiyonu (kalitatif, kantitatif)

Candida Spp  
Aspergillus Spp

Hücrel immünite sorunları

Cryptococcus Spp.

Metabolik sendromlar

Zygomycetes  
Candida Spp

Maruziyet  
İleri yaş > 70

Aspergillus  
Candida Spp

# Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: A multicenter, prospective, observational study in France (2005–2006)

**Table 1.** Clinical characteristics of 271 patients with invasive *Candida* species infections on admission in intensive care unit, expressed as median (range) values or numbers (%) of patients

|   | All Patients<br>(n = 271) | Isolated Candidemia<br>(n = 107) | Invasive Candidiasis Without<br>Documented Candidemia<br>(n = 87) | Invasive Candidiasis<br>With Candidemia<br>(n = 77) | <i>p</i> <sup>a</sup> |
|---|---------------------------|----------------------------------|---|---|-----------------------|
| Age (yrs)                               | 64 (18–90)                | 63 (18–87)                       | 65 (22–90)  | 65 (30–83)  | 0.8                   |
| Sex: male                               | 163 (60.1)                | 66 (61.7)                        | 51 (58.6)   | 46 (59.7)   | 0.9                   |
| Simplified Acute Physiology Score II    | 49 (0–121)                | 48 (0–121)                       | 50 (15–94)  | 48 (0–119)  | 1                     |
| Sepsis-Related Organ Failure Assessment | 9 (0–22)                  | 10 (0–22)                        | 9 (1–22)  | 9 (0–22)  | 0.5                   |
| Ultimately fatal underlying disease     | 113 (41.7)                | 49 (45.8)                        | 31 (35.6)   | 33 (42.9)   | 0.4                   |
| Rapidly fatal underlying disease        | 29 (10.7)                 | 9 (8.4)                          | 10 (11.5)   | 10 (13.0)   | 0.6                   |
| Surgery                                 | 153 (56.5)                | 49 (45.8)                        | 51 (58.6)   | 53 (68.8)   | 0.007                 |
| Vascular                                | 13 (4.8)                  | 7 (6.5)                          | 1 (1.1)   | 5 (6.5)   | 0.06                  |
| Intra-abdominal                         | 118 (43.5)                | 35 (32.7)                        | 48 (55.2)   | 35 (45.5)   | 0.002                 |
| Others                                  | 46 (17.0)                 | 17 (15.9)                        | 5 (5.7)   | 24 (31.2)   | <0.001                |
| Invasive mechanical ventilation         | 205 (75.6)                | 80 (74.8)                        | 73 (83.9)   | 52 (67.5)   | 0.049                 |
| Central venous catheter                 | 247 (91.1)                | 101 (94.4)                       | 80 (92.0)   | 66 (85.7)   | 0.1                   |
| Implantable drug delivery device        | 15 (5.5)                  | 7 (6.5)                          | 4 (4.6)   | 4 (5.2)   | 0.9                   |
| Urinary catheter                        | 235 (86.7)                | 91 (85.0)                        | 77 (88.5)   | 67 (87.0)   | 0.8                   |
| Prior antibiotherapy                    | 160 (59.0)                | 75 (70.1)                        | 36 (41.4)   | 49 (63.6)   | <0.001                |
| Immunosuppression                       | 57 (21.0)                 | 26 (24.3)                        | 14 (16.1)   | 17 (22.1)   | 0.4                   |
| Chronic renal failure                   | 46 (17.0)                 | 21 (19.6)                        | 12 (13.8)   | 13 (16.9)   | 0.6                   |
| Type 1 diabetes mellitus                | 29 (10.7)                 | 14 (13.1)                        | 6 (6.9)   | 9 (11.7)  | 0.4                   |
| Neutropenia                             | 18 (6.6)                  | 11 (10.3)                        | 1 (1.1)   | 6 (7.8)   | 0.04                  |
| Solid tumor                             | 71 (26.2)                 | 15 (14.0)                        | 31 (35.6)   | 25 (32.5)   | 0.006                 |
| Hematological malignancy                | 21 (7.7)                  | 14 (13.1)                        | 4 (4.6)   | 3 (3.9)   | 0.04                  |
| Current intravenous drug use            | 3 (1.1)                   | 1 (0.9)                          | 1 (1.1)   | 1 (1.3)   | 1                     |

<sup>a</sup>Comparison of patients according to localization of infection: isolated candidemia vs. invasive candidiasis without documented candidemia vs. invasive candidiasis with candidemia.

# Risk Factors for Fluconazole-Resistant *Candida glabrata* Bloodstream Infections

- 76 hasta F-R *C glabrata* BSI
- 68 hasta F-S *C glabrata* BSI
- 512 kontrol

Table 3. Adjusted Risk Factors for *Candida glabrata* Bloodstream Infections

| Variable      | Adjusted OR (95% CI); P Value <sup>a</sup>         |  |
|---------------|--|--|
|               | Fluconazole-Resistant <i>C glabrata</i> Case Group | Fluconazole-Susceptible <i>C glabrata</i> Case Group |
| Time at risk  | 1.0 (1.0-1.0); .16                                 | ...  |
| Therapy       |  |  |
| Cefepime      | 1.6 (0.9-2.9); .09                                 | 2.2 (1.2-3.9); .007                                  |
| Fluconazole   | 2.3 (1.3-4.2); .007                                | 1.2 (0.6-2.4); .53                                   |
| Linezolid     | 4.6 (2.2-9.3); <.001                               | ...  |
| Metronidazole | 1.5 (0.8-2.6); .18                                 | 2.0 (1.1-3.5); .02                                   |
| Vancomycin    | 1.3 (0.7-2.4); .35                                 | 1.3 (0.7-2.3); .34                                   |

Abbreviations: CI, confidence interval; OR, odds ratio; ellipses, variable not included in the multivariate model.

<sup>a</sup> Both case groups were independently compared with the control group.

# İNVAZİF ASPERGİLLOŞİS SIKLIĞI

•Tahmin etmek çok güç

**1.** Kolonizasyon ile enfeksiyonu ayırmak güç

**2.** Rutin otopsi uygulayan merkez çok az

**3.** Non-nötropenik YB hastalarında karakteristik AC

filmi görünümü yok

**4.** YB hastaları için kültür dışı yöntemler yeterince çalışılmamıştır



# Otopsi Çalışmaları

•100 YB hastasında yapılan otopsi çalışmasında 15 İA. 5 i ölüm öncesi tanısız.

Roosen J et al. Mayo Clin Proc 2000; 75:562–7.

•YB yatışı sırasında 1850 hastadan 127 sinde (%6.9) mikrobiyolojik veya histopatolojik aspergillosis kanıtı. Bunların 89 unda (%70) hematolojik hastalık yok

•Gerçek mortalite (%80) beklenen mortaliteden (%48) çok daha fazla.

Meersseman W et al. Am J Respir Crit Care Med 2004;170:621–5

# Aspergillus için Risk Faktörleri

- KOAH: uzun süre steroid kullanımı ile birlikte
- Yüksek doz steroid > 3 hafta (prednisolon > 20 mg/gün)
- KBY: Diyaliz gerektiren
- Karaciğer sirozu
- Boğulma
- Diyabetes mellitus

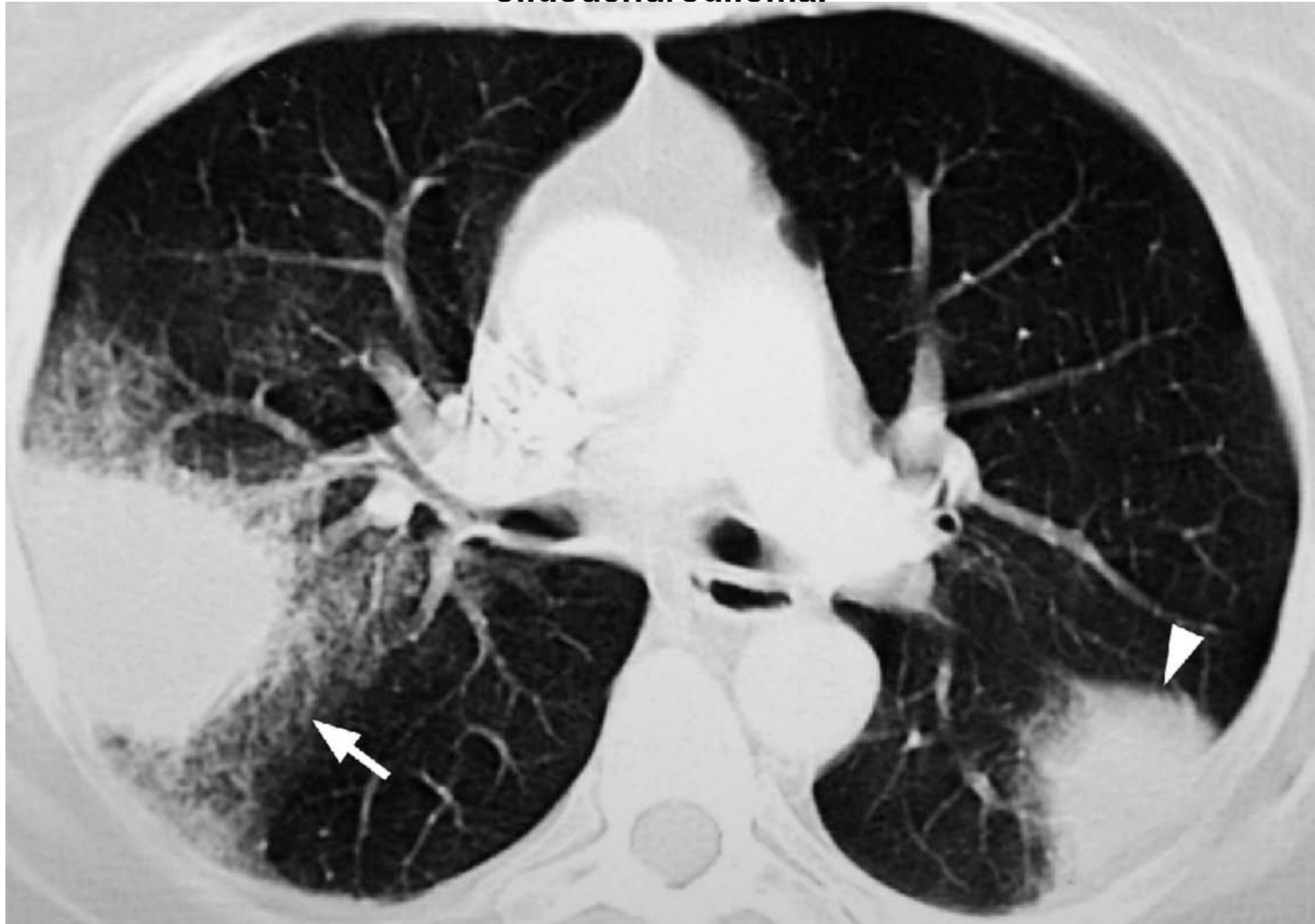
# CT

**Halo bulgusu → en erken bulgudur (hastalığın gelişiminden 5 gün önce).  
Aspergillus için spesifik değil**

**Hilal bulgusu →atelektazi, ARDS ve plevral effüzyonda da görülür**

**YB hastasında CT çekmek her zaman mümkün değil**

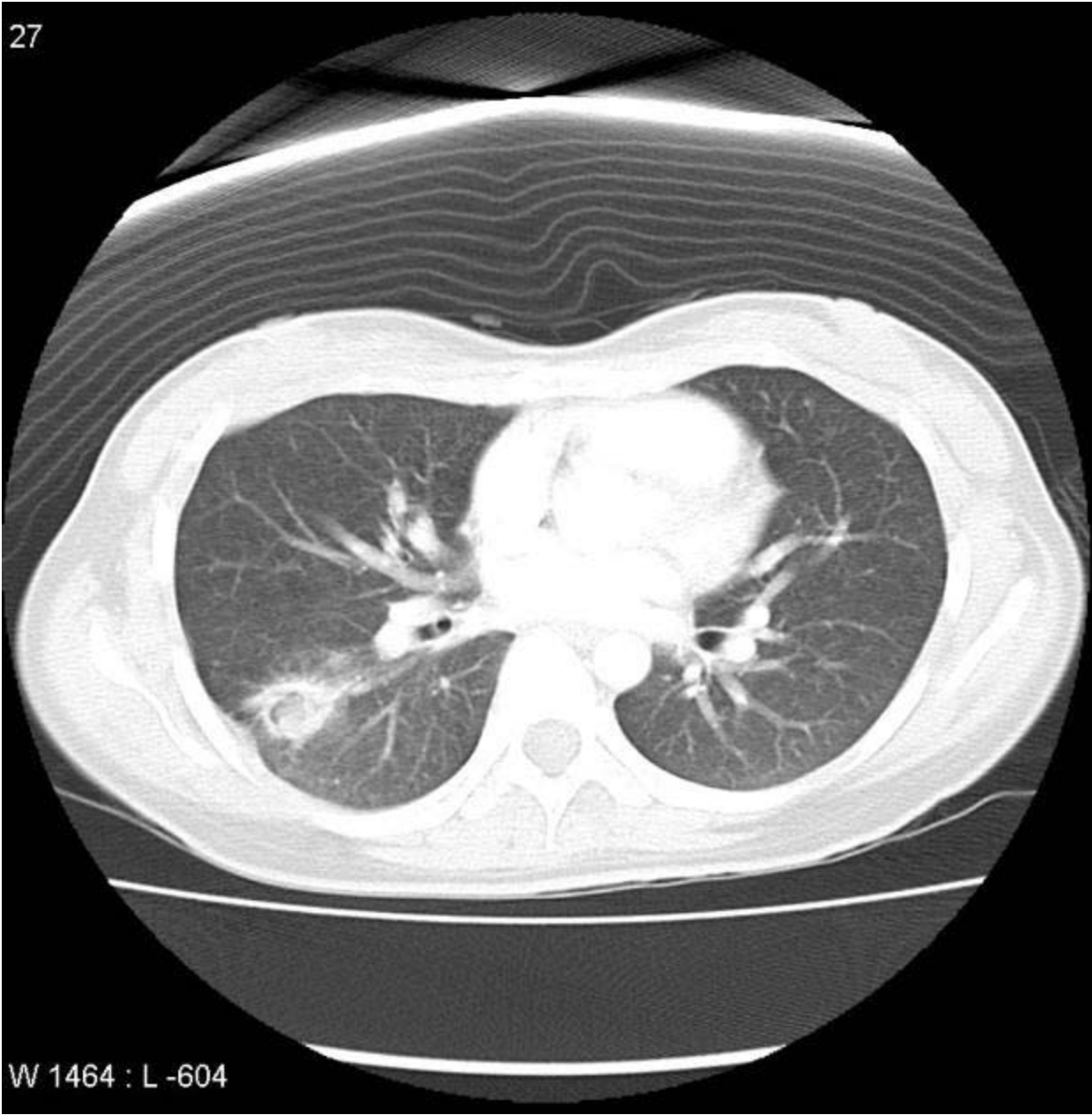
**Transverse CT scan obtained in a 50-year-old woman with invasive pulmonary aspergillosis treated with a high dosage of steroids to reduce cerebral edema from anaplastic oligodendrolioma.**



Pinto P S Radiology 2004;230:109-110

Radiology

27



W 1464 : L -604



# Histopatolojik kanıt

## YB hastası için standart tanı yöntemi

Roosen J et al. Mayo Clin Proc 2000; 75: 562-7 → 100 İA

Meersseman W et al. Am J Respir Crit Care 2004; 170:621-5 →129 İA

**YB hastalarında biyopsi yapmak çoğu kez mümkün değildir**

# Kültür

- Düşük sensitivite ve spesifisite.
- İzolasyon birkaç gün sürer.
- Mikrsokopi ve kültür ile olguların % 50 si atlanır.
- Kolonizasyon ? Enfeksiyon ?
- İmmünsupresif hastalarda daha değerli



# Mikroskopi

**PAS, Grocott boyası, hızlı bir teknik,  
ancak Aspergillus için spesifik değil.**

# **Galaktomannan serum düzeyi (Sınır, 0.5-1.5 ng/mL)**

- **Çoğunlukla hematoloji hastalarında çalışılmıştır**
- **Yanlış pozitif (Pip/Taz)**
- **YB hastarında BAL düzeyi serum düzeyinden daha değerlidir**

# Galactomannan in Bronchoalveolar Lavage Fluid

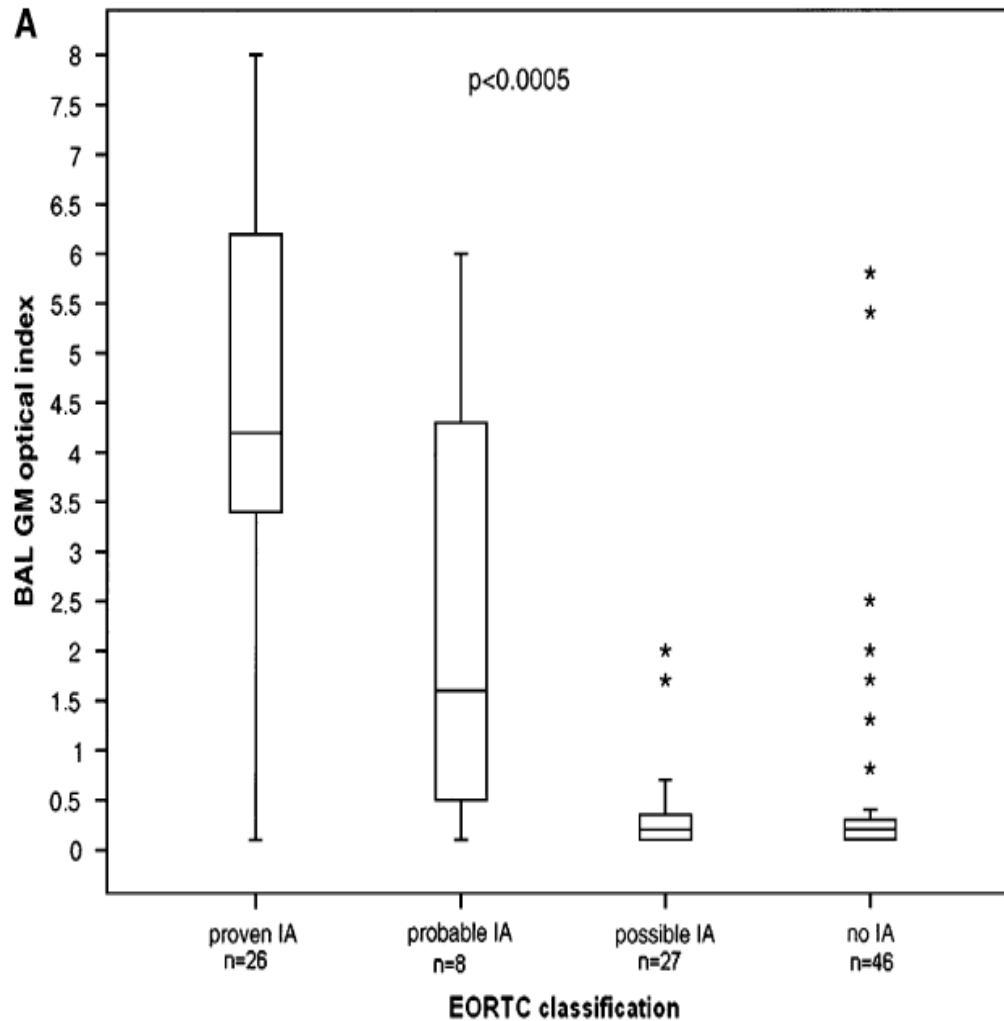
## A Tool for Diagnosing Aspergillosis in Intensive Care Unit Patients

TABLE 3. GALACTOMANNAN AND CULTURE RESULTS IN 72 PATHOLOGY-CONTROLLED CASES\*

|                                       | No. of Patients                 |                                     | Total |
|---------------------------------------|---------------------------------|-------------------------------------|-------|
|                                       | Invasive Aspergillosis (n = 26) | No Invasive Aspergillosis† (n = 46) |       |
| Serum galactomannan, no.‡             |                                 |                                     |       |
| Positive                              | 11                              | 3                                   | 14    |
| Negative                              | 15                              | 43                                  | 58    |
| Total                                 | 26                              | 46                                  | 72    |
| BAL galactomannan, no.‡               |                                 |                                     |       |
| Positive                              | 23                              | 6                                   | 29    |
| Negative                              | 3                               | 40                                  | 43    |
| Total                                 | 26                              | 46                                  | 72    |
| BAL culture, direct examination, no.§ |                                 |                                     |       |
| Positive (%)                          | 15 (58)                         | 14 (30)                             | 29    |
| Negative (%)                          | 11 (42)                         | 32 (70)                             | 43    |
| Total                                 | 26                              | 46                                  | 72    |

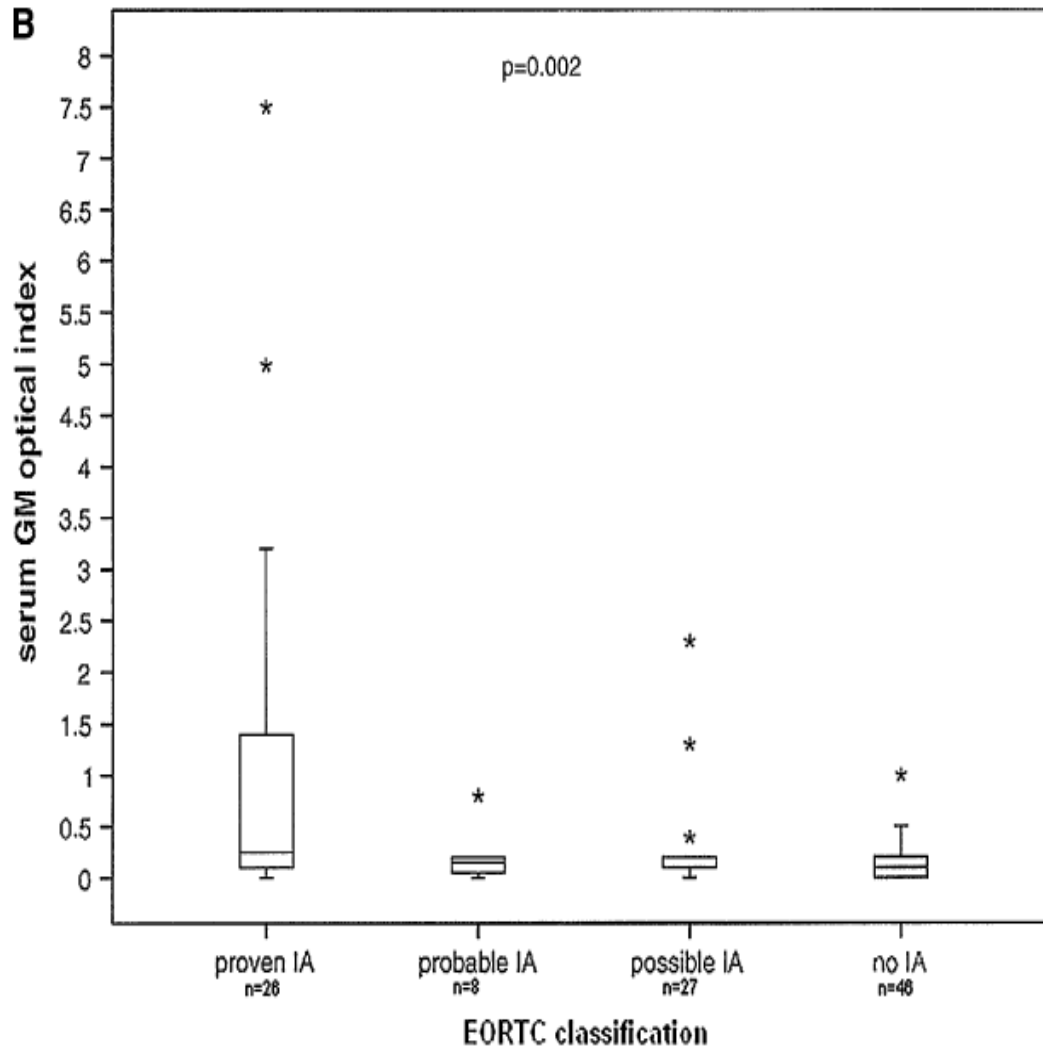
# Galactomannan in Bronchoalveolar Lavage Fluid

A Tool for Diagnosing Aspergillosis in Intensive Care Unit Patients



# Galactomannan in Bronchoalveolar Lavage Fluid

## A Tool for Diagnosing Aspergillosis in Intensive Care Unit Patients



# Beta-(1,3)D-glucan

- Çokça yanlış pozitif sonuç (albumin, hemodiyaliz, bakteriyal enfeksiyon).
- Aspergillus için spesifik değil
- Dışlama kriteri olarak kullanılabilir

# **Aspergillus Kolonizasyonu Ne Demek?**

**Table 3** Comparison of outcome measures between patients with definite/probable IPA and patients with airway colonization

| Outcome                | All patients<br>(n = 104) | Definite/<br>probable IPA<br>(n = 29) | Airway<br>colonization<br>(n = 75) | <i>P</i> <sup>a</sup> |
|------------------------|---------------------------|---------------------------------------|------------------------------------|-----------------------|
| ICU LOS<br>(mean) (d)  | 15.4                      | 20.1                                  | 13.9                               | .11                   |
| Predicted<br>mortality | 35.5%                     | 35.8%                                 | 35.5%                              | .95                   |
| Actual<br>mortality    | 50%                       | 59%                                   | 47%                                | .38                   |

<sup>a</sup> All comparisons were done using Student *t* test except actual mortality, which was done using Fisher exact test.



# Nonhematolojik YB Hastalarında Aspergillosis

Dahili YB. Retrospektif çalışma. 1850 hastadan 127 sinde (%6.9) Aspergillosis. Hastaların % 70 i hematolojik malignite değil.

TABLE 2. CLINICAL CHARACTERISTICS OF PATIENTS WITHOUT HEMATOLOGICAL MALIGNANCY WITH PROVEN OR PROBABLE IA

|                        | All<br>(n = 67) | COPD<br>(n = 33) | Systemic<br>Disease<br>(n = 14) | Liver<br>Cirrhosis<br>(n = 3) | Solid Organ<br>Transplants<br>(n = 9) | Other<br>(n = 8) |
|------------------------|-----------------|------------------|---------------------------------|-------------------------------|---------------------------------------|------------------|
| Age, yr, mean          | 65              | 69               | 60                              | 55                            | 51                                    | 73               |
| SAPS II, mean          | 52              | 49               | 50                              | 64                            | 47                                    | 66               |
| Predicted mortality, % | 48              | 43               | 44                              | 71                            | 40                                    | 73               |
| Observed mortality, %  | 91              | 85               | 93                              | 100                           | 100                                   | 100              |
| Length of stay, d      | 21              | 23               | 18                              | 13                            | 22                                    | 14               |
| Culture positive*      | 56/67           | 31/33            | 10/14                           | 1/3                           | 6/9                                   | 8/8              |
| Asp Ag** Positive*     | 27/51           | 12/25            | 7/11                            | 0/0                           | 4/9                                   | 4/6              |
| Autopsy positive*      | 27/41           | 12/19            | 6/9                             | 3/3                           | 3/6                                   | 3/4              |

\*Tested positive/tested.

\*\* Serum aspergillus antigen (galactomannan assay by means of ELISA).

# Tedavi

**Table 2** Treatment options with antifungal drugs for IPA in critically ill patients in the ICU

| Setting                | First choice  | Alternatives  |
|------------------------|---|---|
| Primary therapy of IPA | Voriconazole 6 mg/kg q 12 h i.v. on day 1, then 4 mg/kg q 12 h i.v.<br>or<br>Voriconazole 400 mg q 12 h oral on day 1, then 200 mg q 12 h oral <sup>a</sup> | Liposomal amphotericin B 3-5 mg/kg/day i. v.<br><br>or<br>Amphotericin B deoxycholate 1 mg/kg/day i. v.<br><br>or<br>Caspofungin 70 mg i.v. on day 1, then 50 mg/day i. v. <sup>b</sup> |

<sup>a</sup> Oral administration is recommended only in patients with intact intestinal absorption; <sup>b</sup> In patients with moderate to severe hepatic failure, dose reduction is recommended to 35 mg/day i. v.

# Diğer Flamentöz Funguslar

- Fusariosis
- Zygomycosis
- Scedosporiosis
- Cryptococcosis
- Diğerleri
  - ÇOK NADİR
  - HIV, Organ ve kemik iliği nakli olan hastalarda düşün

# YOĞUN BAKIMDA CANDİDA EPİDEMİYOLOJİ

- Son 20 yılda Candida spp ile enfeksiyonlarda ciddi artış
- Hastanede yatan hastaların %1 - %8 inde ve YB hastalarının %10 unda  
(Eggimann P et al. Lancet Infect Dis 2003; 3:685–702).
- YB hastalarının nosokomial enfeksiyonlarının % 15-20 si kandidiazise bağlı.  
(Eggimann P et al. Lancet Infect Dis 2003; 3:685–702; Magnason S et al. Acta Anaesthesiol Scand 2008;52: 1238–45)

# YOĞUN BAKIMDA CANDİDA EPİDEMİYOLOJİ

- Kandidemilerin % 80 i invazif damar yolu varlığında oluşur.
- Kandidemilerin %33 - %55 i YB hastalarında oluşur ve mortalite % 5 – 71 arasında.

**Ben-Ami R et al. J Clin Microbiol 2008;46:2222–6**

**Bouza E et al. Int J Antimicrob Agents 2008;32(Suppl 2):S87–91.**

# Hangi Candida?

- En sık Candida Albicans
- C. Parapsilosis Avrupada en sık 2. ajan
- C. Glabrata Kuzey Amerika ve Avustralyada en sık 2. ajan
- Abdominal enfeksiyon; çoğunlukla C. Albicans

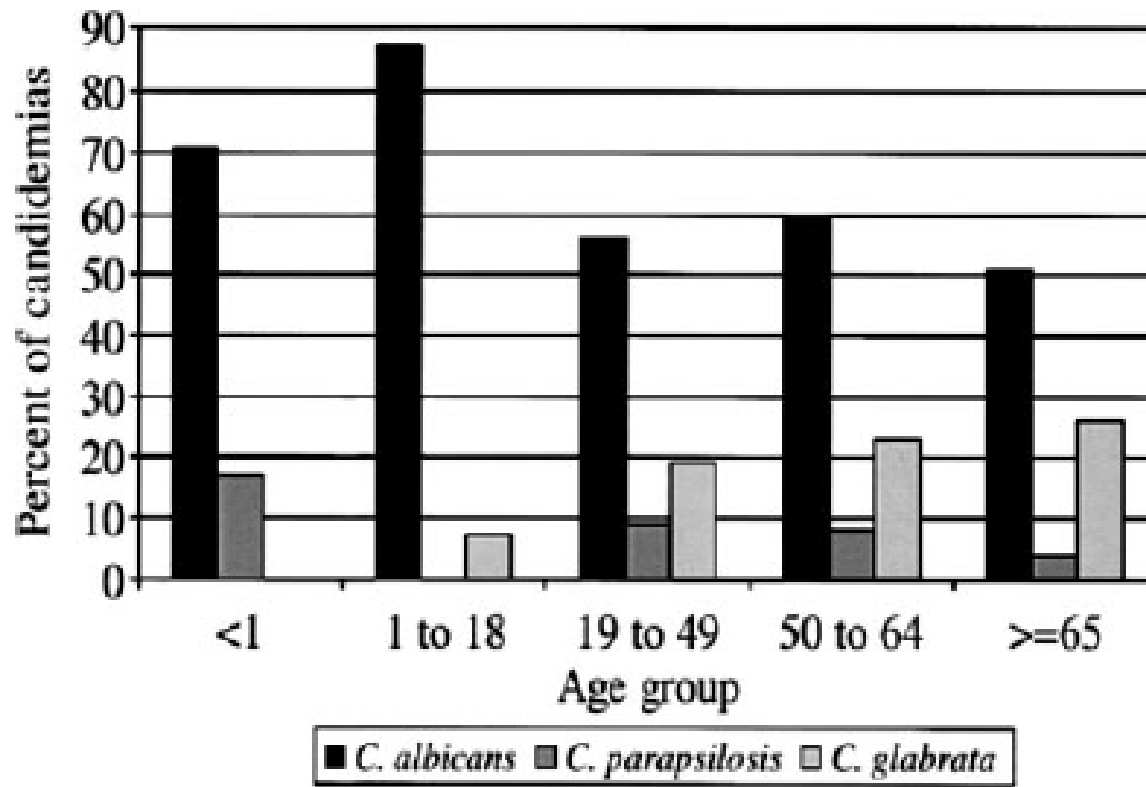


FIG. 2. Percentages of all candidemias due to selected *Candida* species in each group. Data are from the Emerging Infections and the Epidemiology of Iowa Organisms survey, 1998 to 2001 ( $P = 0.02$  [for trend of increased frequency of *C. glabrata* with increasing age]). (Adapted from reference 205.)

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

|                                 | No. (%) <sup>a</sup> |                |                         |                         |                         |                        |                        |                         |
|---------------------------------|----------------------|----------------|-------------------------|-------------------------|-------------------------|------------------------|------------------------|-------------------------|
|                                 | 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) <sup>b</sup> | 851 (66)                | 345 (56.8) <sup>b</sup> | 165 (57.9)             | 41 (46.1) <sup>b</sup> | 464 (65.6)              |
| Abdominal                       | 1392 (19.6)          | 778 (21.1)     | 93 (21.8)               | 228 (17.7) <sup>b</sup> | 101 (16.6)              | 50 (17.5)              | 16 (18)                | 126 (17.8)              |
| Bloodstream                     | 1071 (15.1)          | 546 (14.8)     | 53 (12.4)               | 139 (10.8) <sup>b</sup> | 157 (25.9) <sup>b</sup> | 49 (17.2)              | 16 (18)                | 111 (15.7)              |
| Renal/urinary tract             | 1011 (14.3)          | 411 (11.2)     | 84 (19.7) <sup>b</sup>  | 222 (17.2) <sup>b</sup> | 135 (22.2) <sup>b</sup> | 33 (11.6)              | 15 (16.9)              | 111 (15.7) <sup>b</sup> |
| Skin                            | 467 (6.6)            | 242 (6.6)      | 37 (8.7)                | 73 (5.7)                | 26 (4.3)                | 30 (10.5)              | 8 (9.0)                | 51 (7.2)                |
| Catheter-related                | 332 (4.7)            | 171 (4.6)      | 21 (4.9)                | 73 (5.7)                | 16 (2.6)                | 15 (5.3)               | 4 (4.5)                | 32 (4.5)                |
| CNS                             | 208 (2.9)            | 100 (2.7)      | 20 (4.7)                | 40 (3.1)                | 14 (2.3)                | 11 (3.9)               | 4 (4.5)                | 19 (2.7)                |
| Others                          | 540 (7.6)            | 289 (7.8)      | 31 (7.3)                | 87 (6.7)                | 62 (10.2)               | 22 (7.7)               | 14 (15.7) <sup>b</sup> | 35 (5.0) <sup>b</sup>   |
| Microorganisms                  |                      |                |                         |                         |                         |                        |                        |                         |
| Positive isolates               | 4947 (69.8)          | 2678 (72.7)    | 357 (83.8) <sup>b</sup> | 719 (55.7) <sup>b</sup> | 457 (75.3)              | 204 (71.6)             | 54 (60.7)              | 478 (67.6) <sup>b</sup> |
| Gram-positive                   | 2315 (46.8)          | 1311 (49.0)    | 185 (51.8)              | 273 (38.0) <sup>b</sup> | 252 (55.1)              | 104 (51.0)             | 27 (50.0)              | 163 (34.1) <sup>b</sup> |
| <i>Staphylococcus aureus</i>    | 1012 (20.5)          | 525 (19.6)     | 77 (21.6)               | 138 (19.2)              | 123 (26.9) <sup>b</sup> | 56 (27.5) <sup>b</sup> | 16 (29.6)              | 77 (16.1)               |
| MRSA                            | 507 (10.2)           | 233 (8.7)      | 37 (10.4)               | 79 (11.0)               | 80 (17.5) <sup>b</sup>  | 19 (9.3)               | 11 (20.4) <sup>b</sup> | 48 (10.0)               |
| <i>S epidermidis</i>            | 535 (10.8)           | 301 (11.2)     | 43 (12)                 | 67 (9.3)                | 56 (12.3)               | 17 (8.3)               | 8 (14.8)               | 43 (9.0)                |
| <i>Streptococcus pneumoniae</i> | 203 (4.1)            | 127 (4.7)      | 16 (4.5)                | 24 (3.3)                | 20 (4.4)                | 5 (2.5)                | 3 (5.6)                | 8 (1.7) <sup>b</sup>    |
| VSE                             | 352 (7.1)            | 250 (9.3)      | 35 (9.8)                | 17 (2.4) <sup>b</sup>   | 24 (5.3) <sup>b</sup>   | 9 (4.4)                | 0 <sup>b</sup>         | 17 (3.6) <sup>b</sup>   |
| VRE                             | 186 (3.8)            | 113 (4.2)      | 16 (4.5)                | 15 (2.1) <sup>b</sup>   | 22 (4.8)                | 10 (4.9)               | 0                      | 10 (2.1)                |
| Other                           | 319 (6.4)            | 184 (6.9)      | 15 (4.2)                | 29 (4.0) <sup>b</sup>   | 48 (10.5)               | 19 (9.3)               | 4 (7.4)                | 20 (4.2)                |
| Gram-negative                   | 3077 (62.2)          | 1573 (58.7)    | 258 (72.3) <sup>b</sup> | 510 (70.9) <sup>b</sup> | 228 (49.9) <sup>b</sup> | 122 (59.8)             | 31 (57.4)              | 365 (74.3) <sup>b</sup> |
| <i>Escherichia coli</i>         | 792 (16.0)           | 458 (17.1)     | 53 (14.8)               | 103 (14.3)              | 65 (14.2)               | 27 (13.2)              | 6 (11.1)               | 80 (16.7)               |
| <i>Enterobacter</i>             | 345 (7.0)            | 184 (6.9)      | 29 (8.1)                | 62 (8.6)                | 37 (8.1)                | 7 (3.4)                | 4 (7.4)                | 22 (4.6)                |
| <i>Klebsiella</i> species       | 627 (12.7)           | 261 (9.7)      | 76 (21.3) <sup>b</sup>  | 116 (16.1) <sup>b</sup> | 41 (9)                  | 24 (11.8)              | 10 (18.5)              | 99 (20.7) <sup>b</sup>  |
| <i>Pseudomonas</i> species      | 984 (19.9)           | 458 (17.1)     | 103 (28.9) <sup>b</sup> | 189 (26.3) <sup>b</sup> | 59 (12.9)               | 30 (14.7)              | 8 (14.8)               | 137 (28.7) <sup>b</sup> |
| <i>Acinetobacter</i> species    | 435 (8.8)            | 149 (5.6)      | 61 (17.1) <sup>b</sup>  | 99 (13.8) <sup>b</sup>  | 17 (3.7)                | 9 (4.4)                | 8 (14.8) <sup>b</sup>  | 92 (19.2) <sup>b</sup>  |
| Other                           | 840 (17.0)           | 487 (18.2)     | 54 (15.1)               | 121 (16.8)              | 52 (11.4) <sup>b</sup>  | 42 (20.6)              | 11 (20.4)              | 73 (15.3)               |
| ESBL-producing                  | 93 (1.9)             | 47 (1.8)       | 7 (2.0)                 | 21 (2.9)                | 1 (0.2) <sup>b</sup>    | 0                      | 1 (1.9)                | 16 (3.3)                |
| Anaerobes                       | 222 (4.5)            | 142 (5.3)      | 12 (3.4)                | 10 (1.4) <sup>b</sup>   | 36 (7.9)                | 7 (3.4)                | 1 (1.9)                | 14 (2.9)                |
| Other bacteria                  | 76 (1.5)             | 33 (1.2)       | 7 (2.0)                 | 14 (1.9)                | 4 (0.9)                 | 4 (2.0)                | 3 (5.6)                | 11 (2.3)                |
| Fungi                           |                      |                |                         |                         |                         |                        |                        |                         |
| <i>Candida</i>                  | 843 (17)             | 495 (18.5)     | 66 (18.5)               | 92 (12.8) <sup>b</sup>  | 83 (18.2)               | 26 (12.7)              | 6 (11.1)               | 75 (15.7)               |
| <i>Aspergillus</i>              | 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) <sup>b</sup>   | 22 (4.8)                | 8 (3.9)                | 2 (3.7)                | 14 (2.9)                |



# Fungal Kolonizasyon

- 1699 yoğun bakım hastası (non nütropenik)
  - 883 hasta kandida kolonizasyonu

Kolonizasyon: Tam steril olmayan örneklerde *Candida* spp olması (orofarinx, mide, idrar, trakeal aspirat)

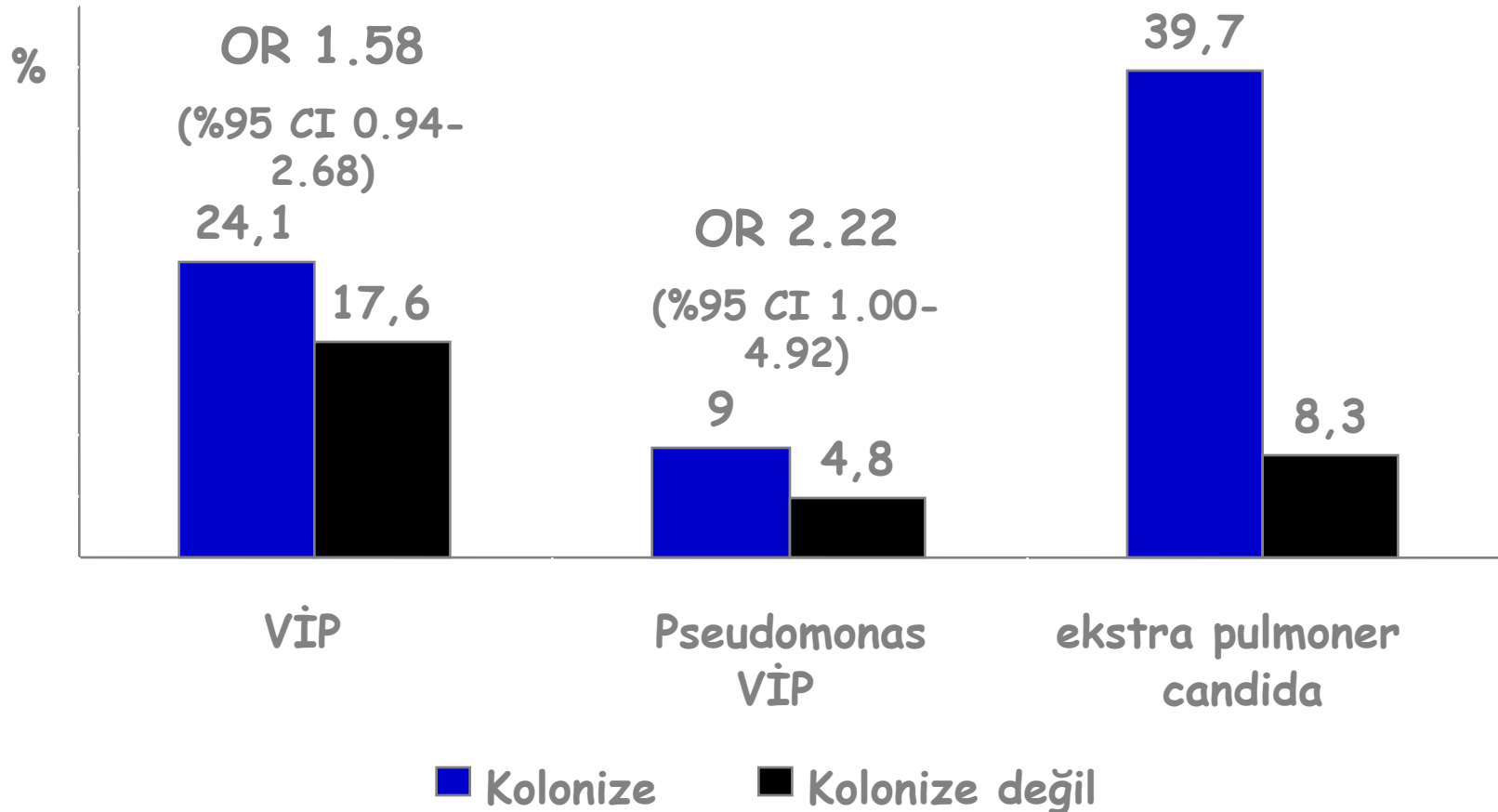
Tek bir odakta üreme

Orofarinx ve mide tek kaynak sayılır

# Solunum Sisteminin Candida Kolonizasyonu ve VIP gelişimi

*Azoulay E et al, Chest, 2006*

803 immunsuprese olmayan YB hastası ve MV > 2 gün.



# Candida Kolonizasyonunun Varlığı Tedaviyi Yönlendirmekte Yetersizdir

- Steril olmayan izolatlara oranla kandan izole edilen ajanların çoğunluğu *Candida glabrata* (16/46 ve 106/1062;  $p < 0.001$ ),
- Benzer olarak kan izolatlarının çoğunluğu F-R dir (15/46 ve 101/1062;  $p < 0.001$ ).

Table 3 Distribution and fcz-sensitivity of *Candida* spp. from blood and non-sterile sites.

|   | Blood     | Non-sterile |
|---|-----------|-------------|
| No of <i>C. albicans</i> isolates (%)                         | 25 (54.3) | 848 (79.8)  |
| No of <i>C. glabrata</i> isolates (%)                         | 16 (34.8) | 106 (10.0)  |
| No of non- <i>albicans</i> /non- <i>glabrata</i> isolates (%) | 5 (10.9)  | 108 (10.2)  |
| No fcz-sensitive (%)  | 31 (67.4) | 961 (90.5)  |
| No fcz SDD/resistant (%)                                      | 15 (32.6) | 101 (9.5)   |

# Candida Kolonizasyonunun Varlığı Tedaviyi Yönlendirmekte Yetersizdir

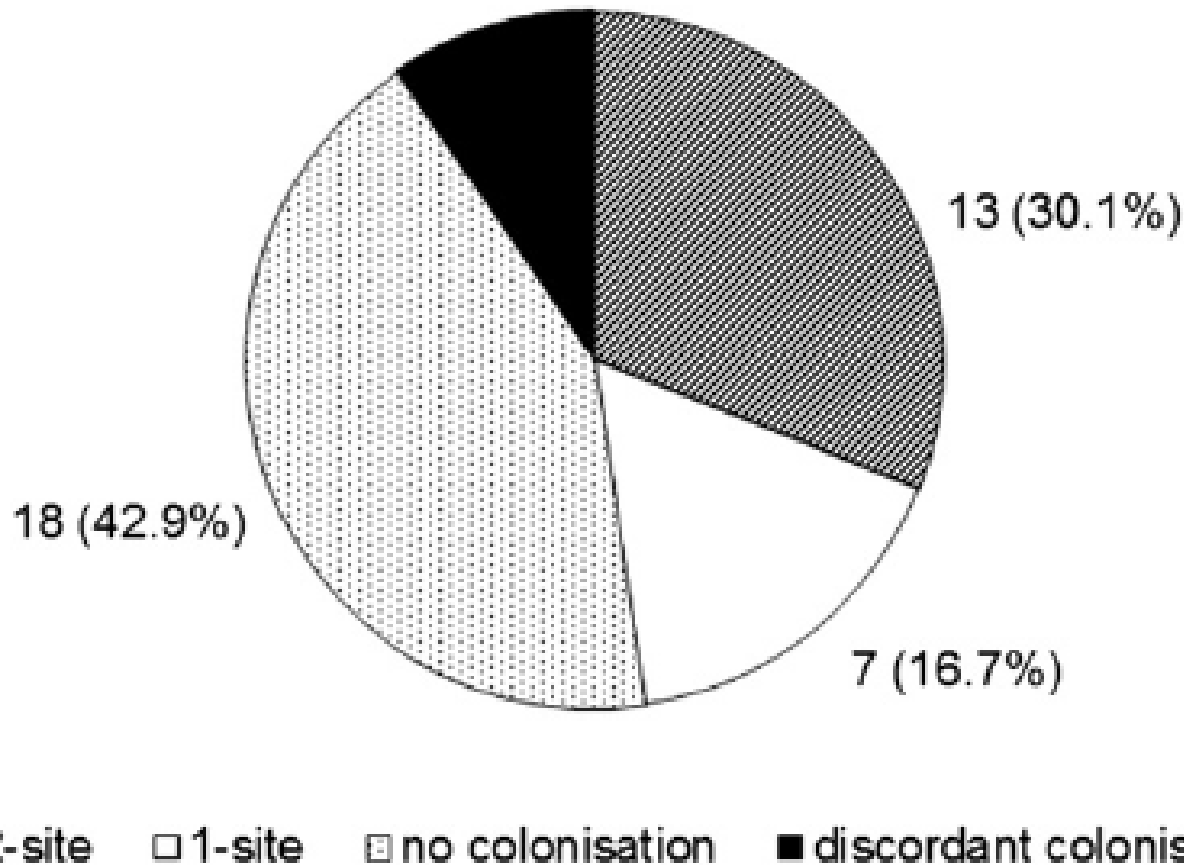


Figure 1 Number of candidaemic patients (%) with prior non-sterile site colonisation at first candidaemic episode.

# Candida Skoru

- Mevcut yatışıta cerrahi 1 puan
  - Birden fazla alanda kolonizasyon 1 puan
  - TPN 1 puan
  - Ağır sepsis 2 puan
- 
- Skor  $\geq 3$  puan yüksek risk....empirik tedavi

# Non n6tropenik YB hastalarında İnvazif Candidiazisi Saptamak İin Y6ntemler

## Tahmin Kuralı

- YB da > 4 g6n kalan 2890 hasta
- En iyi tahmin iin kombinasyon:
  - Sistemik antibiyotik kullanımı veya SVK varlıđı ve aŐađıdakilerden en az 2 si.
    - TPN,
    - Major cerrahi,
    - Pankreatit
    - Steroid veya immunsupresif ajan kullanımı.
- Bu kural ile sensitivite %34, spesifisite %90, pozitif predictive value %10 ve negatif predictive value %97
- Klinisyenler iin bir dıŐlama kriteri .

# Non nütropenik YB hastalarında İnvazif Candidiazisi Saptamak İçin Yöntemler

## CANDİDA SKORU

- YB > 7 gün kalmış 1107 hastada prospektif çalışma
- CS $\geq$ 3 İC için yüksek risk faktörü
- İC=%2.3 eğer CS<3
- (1–3)-Beta-D-glukan İC için bağımsız risk faktörü (odds ratio 1.004, 95% CI 1.0 –1.007)

# FUNGAL ENFEKSİYONLARIN TANISI

- Hızlı ve uygun antifungal tedavi mortaliteyi azalttığı için hızlı tanı son derece önemlidir.
- Ne yazık ki Fungal enfeksiyonların tanısı zordur ve uzun zaman alır.
- Aslında kan kültürlerinin sensitivitesi düşüktür. (< %50) (Reiss E et al. *Clin Microbiol Rev* 1993, 6:311-323), ve çoğunlukla çok geç gelir (Morris AJ et al. *J Clin Microbiol* 1996, 34:1583-1585)



# FUNGAL ENFEKSİYONLARIN TANISI

- YB hastalarında doku örneği almak çoğu kez mümkün değildir.
- Radyolojik bulgular enfeksiyonun geç döneminde çıkar.
- YB hastaları için spesifik tanı kriterleri yoktur
- Sensitif ve spesifik tanı yöntemlerine ihtiyaç var→ Kültür dışı tanı yöntemleri dolaşan fungal metabolitlerin, antijenlerin ve fungal DNA nın saptanmasına yöneliktir.

# ANTİJEN - ANTİKOR TESTLERİ

**Ticari olarak 2 test vardır:**

- Mannan antijen testi (Biorad) ve**
- Beta D-glukan testi.**

# ANTİJEN - ANTİKOR TESTLERİ

## Mannan antijen testi

•Candida duvarında var olan bir maddedir ve serumda saptanabilir.

**Candida-spesifik bir testtir.**

Serum veya plazmada çalışılır.

•Kanda kısa sürede yok olduğu için riskli dönemlerde haftada 2 – 3 kez çalışılması gerekir.

# ANTİJEN - ANTİKOR TESTLERİ

- Mannan -

- Serumda mannan saptanmasının sensitivitesi % 60, mannan antikorlarının ki % 60 ve her 2 testin birden kullanılmasının ki % 89 dur.
- Her 2 testin spesifisitesi > % 90.
- Ek çalışmalar gerekir

# ANTİJEN - ANTİKOR TESTLERİ

- Beta-D-glukan -

- Bir çok fungusun ancak özellikle Candida, aspergillus ve pneumocystis duvarında bulunan bir maddedir.

- **Candida Spesifik değildir.**

- **Çalışmalar yetersiz**

## $\beta$ - (1,3)-D-glukan

- **Negatif predictive value çok iyidir bu nedenle invazif candidiazis için bir dışlama kriteridir.**
- **YB hastaları ile ilgili çalışmalar yetersiz**

TABLE 11. Trends in in vitro resistance to fluconazole among *Candida* spp. determined by CLSI disk diffusion testing over a 6.5-year period (ARTEMIS DISK Surveillance Program, 1997–2003)<sup>a</sup>

| Species                          | Isolates resistant to fluconazole (zone $\leq$ 14 mm) <sup>b</sup> |      |          |      |          |      |          |      |          |      |          |      |
|----------------------------------|--|------|----------|------|----------|------|----------|------|----------|------|----------|------|
|                                  | 1997–1998  |      | 1999     |      | 2000     |      | 2001     |      | 2002     |      | 2003     |      |
|                                  | <i>n</i>   | %    | <i>n</i> | %    | <i>n</i> | %    | <i>n</i> | %    | <i>n</i> | %    | <i>n</i> | %    |
| <i>C. albicans</i>               | 16,514   | 0.8  | 14,677   | 0.8  | 7,961    | 1.5  | 14,268   | 1.0  | 15,147   | 1.5  | 20,576   | 1.4  |
| <i>C. glabrata</i>               | 2,475  | 18.5 | 2,047    | 22.8 | 1,112    | 14.3 | 2,431    | 18.3 | 2,635    | 14.7 | 3,974    | 16.9 |
| <i>C. tropicalis</i>             | 1,036  | 4.2  | 1,117    | 3.5  | 843      | 3.1  | 1,634    | 3.0  | 1,838    | 6.6  | 2,487    | 5.0  |
| <i>C. parapsilosis</i>           | 955  | 2.0  | 1,028    | 2.8  | 650      | 2.9  | 1,501    | 4.2  | 1,632    | 3.9  | 2,406    | 3.0  |
| <i>C. krusei</i>                 | 372  | 56.5 | 459      | 71.5 | 376      | 68.1 | 544      | 70.4 | 639      | 78.9 | 884      | 80.2 |
| <i>C. guilliermondii</i>         | 111  | 6.3  | 168      | 9.5  | 88       | 26.1 | 163      | 11.7 | 239      | 10.5 | 260      | 8.1  |
| <i>C. lusitaniae</i>             | 115  | 2.6  | 99       | 4.0  | 62       | 1.6  | 122      | 6.6  | 131      | 4.6  | 211      | 2.4  |
| <i>C. kefyr</i>                  | 34   | 0.0  | 84       | 4.8  | 64       | 3.1  | 86       | 2.3  | 87       | 5.7  | 171      | 2.9  |
| <i>C. rugosa</i>                 | 7  | 28.6 | 7        | 14.3 | 21       | 42.9 | 151      | 30.5 | 150      | 66.0 | 116      | 61.2 |
| <i>C. famata</i>                 | 19   | 47.4 | 51       | 9.8  | 53       | 13.2 | 54       | 14.8 | 110      | 10.9 | 89       | 11.2 |
| <i>Candida</i> spp. <sup>c</sup> | 894  | 15.5 | 1,260    | 7.1  | 437      | 10.1 | 722      | 9.6  | 1,953    | 5.2  | 1,605    | 11.4 |

<sup>a</sup> Isolates from all specimen types and all hospital locations in 127 institutions. Data are from the study of Pfaller et al. (221).

<sup>b</sup> Fluconazole disk diffusion testing performed in accordance with CLSI guideline M44-A (170). *n*, number of isolates.

<sup>c</sup> Species not identified.

TABLE 20. Delay in treatment of *Candida* bloodstream infections is a potential risk factor for hospital mortality<sup>a</sup>

| Patient stratum     | No. of patients | % Mortality        |          |
|---------------------|-----------------|--------------------|----------|
|                     |                 | Delay <sup>b</sup> | No delay |
| All                 | 157             | 33.1               | 11.1     |
| APACHE II $\leq$ 15 | 90              | 23.5               | 0.0      |
| APACHE II $>$ 15    | 67              | 46.0               | 25.0     |

<sup>a</sup> Data compiled from the study of Morrell et al. (166).

<sup>b</sup> Delay in administering systemic antifungal therapy of  $\geq$ 12 h after the first positive blood culture was drawn.



TABLE 21. Impact of inadequate antifungal therapy on mortality attributable to candidemia, 1998 to 2000<sup>a</sup>

| Treatment category                | Attributable mortality (%) |           |
|-----------------------------------|----------------------------|-----------|
|                                   | Connecticut                | Baltimore |
| Overall                           | 19                         | 24        |
| Adequate treatment <sup>b</sup>   | 11                         | 16        |
| Inadequate treatment <sup>c</sup> | 31                         | 41        |

<sup>a</sup> Data compiled from the study of Morgan et al. (164).

<sup>b</sup> Any systemically active antifungal agent for  $\geq 7$  days after first positive blood culture.

<sup>c</sup> Less than 7 days of therapy (30 to 39% of total). Patients who did not survive a minimum of 3 days after a positive blood culture were not included in the analysis.

# Direnç

- C. Kruzei.....Flukanazole dirençli
- C. Glabrata....Kolayca triazol direnci gelişir
- C. Albikans, tropikalıs ve parapsilosis nadir flukanozol direnci.

# Direnç

- *C. parapsilosis* ve *C. guilliermondii* yeni ekinokandinlere daha az hassas

TABLE 15. In vitro activities of anidulafungin, caspofungin, and micafungin: results from two large multicenter surveys

| Species                  | Antifungal agent | No. and in vitro susceptibility ( $\mu\text{g/ml}$ ) of isolates by study <sup>a</sup> |                   |                   |   |                   |                   |
|--------------------------|------------------|--|-------------------|-------------------|---|-------------------|-------------------|
|                          |                  | Pfaller et al. (220, 224, 230) <sup>b</sup>  |                   |                   | Ostrosky-Zeichner et al. (183) <sup>c</sup> |                   |                   |
|                          |                  | <i>n</i>   | MIC <sub>50</sub> | MIC <sub>90</sub> | <i>n</i>                                    | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>C. albicans</i>       | Anidulafungin    | 1,483  | 0.03              | 0.12              | 733   | 0.03              | 0.03              |
|                          | Caspofungin      |  | 0.03              | 0.06              |   | 0.5               | 0.5               |
|                          | Micafungin       |  | 0.015             | 0.03              |   | 0.03              | 0.03              |
| <i>C. glabrata</i>       | Anidulafungin    | 356  | 0.06              | 0.12              | 458   | 0.03              | 0.13              |
|                          | Caspofungin      |  | 0.03              | 0.06              |   | 0.5               | 1.0               |
|                          | Micafungin       |  | 0.015             | 0.03              |   | 0.03              | 0.06              |
| <i>C. tropicalis</i>     | Anidulafungin    | 269  | 0.03              | 0.06              | 307   | 0.03              | 0.13              |
|                          | Caspofungin      |  | 0.03              | 0.06              |   | 0.5               | 1.0               |
|                          | Micafungin       |  | 0.03              | 0.06              |   | 0.03              | 0.06              |
| <i>C. krusei</i>         | Anidulafungin    | 63   | 0.03              | 0.06              | 50  | 0.06              | 0.13              |
|                          | Caspofungin      |  | 0.06              | 0.25              |   | 1.0               | 2.0               |
|                          | Micafungin       |  | 0.06              | 0.12              |   | 0.13              | 0.25              |
| <i>C. parapsilosis</i>   | Anidulafungin    | 383  | 2.0               | 4.0               | 391   | 2.0               | 2.0               |
|                          | Caspofungin      |  | 0.5               | 1.0               |   | 2.0               | 2.0               |
|                          | Micafungin       |  | 1.0               | 2.0               |   | 1.0               | 2.0               |
| <i>C. guilliermondii</i> | Anidulafungin    | 45   | 1.0               | 2.0               | 9   | 1.0               |                   |
|                          | Caspofungin      |  | 0.5               | 1.0               |   | 1.0               |                   |
|                          | Micafungin       |  | 0.5               | 1.0               |   | 0.5               |                   |
| All <i>Candida</i> spp.  | Anidulafungin    | 2,663  | 0.06              | 2.0               |   |                   |                   |
|                          | Caspofungin      |  | 0.03              | 0.25              |   |                   |                   |
|                          | Micafungin       |  | 0.015             | 1.0               |   |                   |                   |

<sup>a</sup> *n*, number of isolates.

<sup>b</sup> MICs determined in RPMI broth, with a 24-h incubation and a prominent inhibition endpoint.

<sup>c</sup> MICs determined as described in footnote *a* except for a 48-h incubation.

# Antifungal tedavi zamanlaması ve mortalite

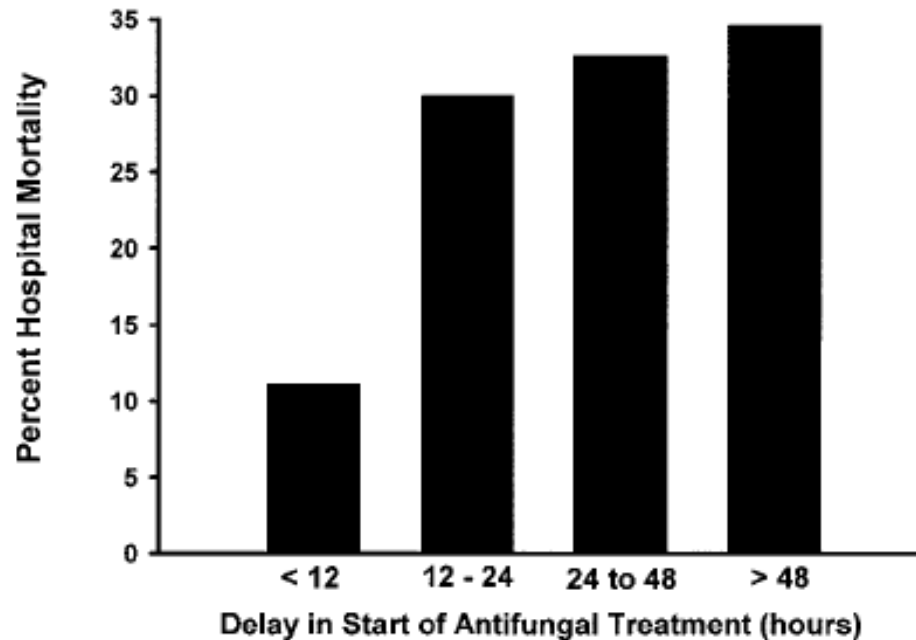


FIG. 1. Relationship between hospital mortality and the timing of antifungal treatment. The timing of antifungal therapy was determined to be from the time when the first blood sample for culture positive for fungi was drawn to the time when antifungal treatment was first administered to the patient.

TABLE 22. Increased hospital costs associated with candidemia<sup>a</sup>

| Category                | Cost (\$) <sup>b</sup> | % of total cost |
|-------------------------|------------------------|-----------------|
| Total                   | 44,536                 | 100             |
| Length of hospital stay | 37,681                 | 84.6            |
| Antifungal therapy      | 4,710                  | 10.5            |
| Diagnostic procedures   | 1,513                  | 3.4             |
| Adverse drug reactions  | 610                    | 1.4             |

<sup>a</sup> Data compiled from the study of Rentz et al. (246).

<sup>b</sup> In 1997 dollars.

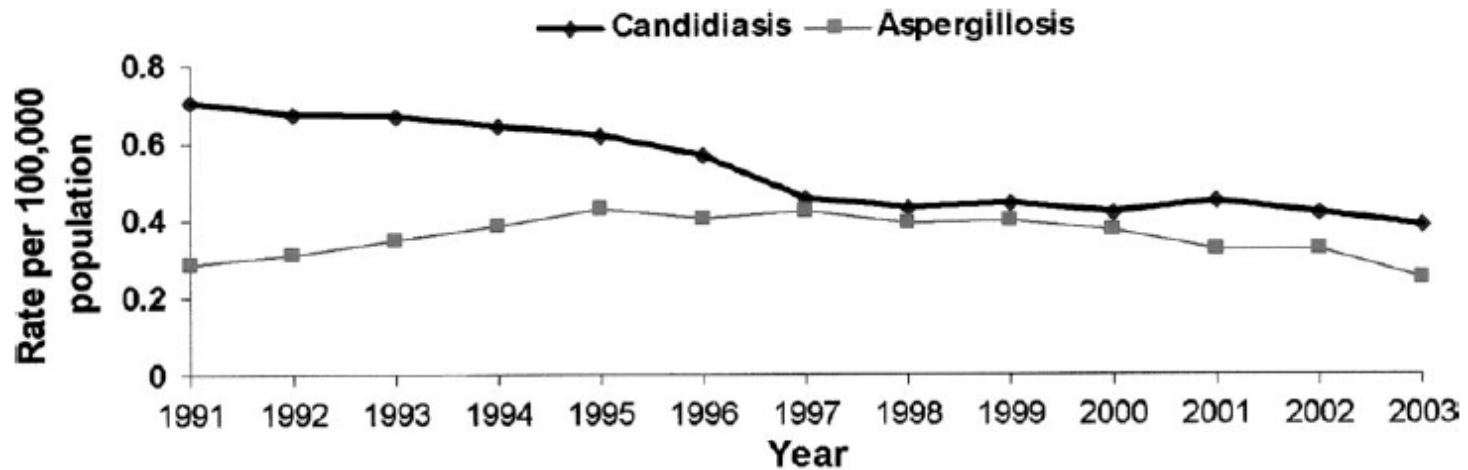
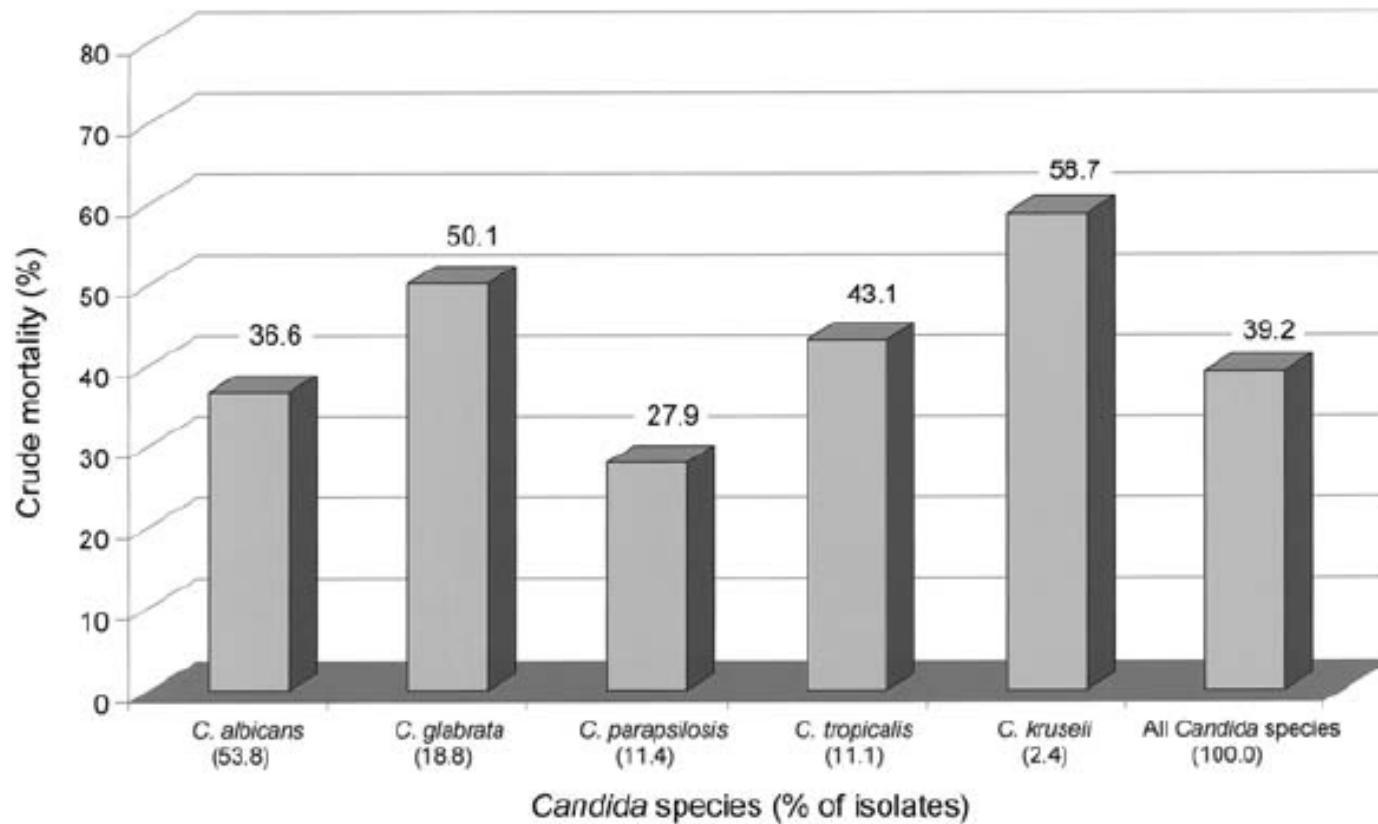


FIG. 1. U.S. crude mortality rates for IC and IA, 1991 to 2003 (NCHS multiple-cause-of-death data from public use files [<http://www.cdc.gov/nchs/>]).

Wisplinghoff H. Clin Infect Dis 2004 Aug 1;39(3):309-17



Distribution of *Candida* species in 1890 cases of *Candida* bloodstream infection and associated crude mortality



**Table 2****Risk factors for hospital mortality on entire ICU cohort with candidaemia**

| Variable   | Dying patients*   | Surviving patients* | Univariate analysis**  |        | Multivariate analysis† |        |
|--|-------------------|---------------------|------------------------|--------|------------------------|--------|
|  |                   |                     | Unadjusted HR (95% CI) | P      | Adjusted HR (95% CI)†† | P      |
| Male sex   | 55/97 (57%)       | 45/76 (59%)         | 1.00 (0.67 to 1.49)    | 0.99   |                        |        |
| Age  | 63.3 ± 16.7 years | 51.1 ± 19.2 years   | 1.03 (1.01 to 1.04)    | <0.001 | 1.03 (1.01 to 1.4)     | <0.001 |
| Antifungal agents prior to diagnosis             | 10/96 (10%)       | 6/76 (8%)           | 1.03 (0.53 to 1.98)    | 0.93   |                        |        |
| Non-receipt of antifungal agents after diagnosis | 20/97 (21%)       | 5/76 (7%)           | 5.17 (3.08 to 8.68)    | <0.001 | 7.90 (3.73 to 16.71)   | <0.001 |
| <i>Candida albicans</i>                          | 43/97 (44%)       | 26/76 (34%)         | 0.73 (0.49 to 1.10)    | 0.13   |                        |        |
| Vascular access device removed or not in place   | 55/80 (69%)       | 64/79 (84%)         | 0.41 (0.26 to 0.67)    | <0.001 |                        |        |
| TPN receipt                                      | 53/96 (55%)       | 26/76 (34%)         | 1.52 (1.02 to 2.28)    | 0.04   |                        |        |
| Haemodialysis                                    | 23/97 (24%)       | 8/76 (11%)          | 1.66 (1.04 to 2.66)    | 0.03   |                        |        |
| Corticosteroid receipt                           | 33/97 (34%)       | 20/76 (26%)         | 1.36 (0.89 to 2.07)    | 0.17   |                        |        |
| Non-multitrauma patient                          | 93/97 (96%)       | 60/76 (79%)         | 3.25 (1.19 to 8.87)    | 0.02   | 6.97 (1.64 to 29.67)   | 0.009  |
| Recent surgery                                   | 71/97 (73%)       | 47/76 (62%)         | 1.24 (0.79 to 1.94)    | 0.35   |                        |        |
| Other healthcare related infections              | 73/97 (75%)       | 55/76 (72%)         | 0.85 (0.53 to 1.35)    | 0.49   |                        |        |
| Ventilation at day 1                             | 82/96 (85%)       | 55/76 (72%)         | 1.51 (0.86 to 2.67)    | 0.15   | 4.03 (1.93 to 8.41)    | <0.001 |
| Sepsis at day 1                                  | 86/97 (89%)       | 60/76 (79%)         | 1.33 (0.71 to 2.49)    | 0.37   |                        |        |
| Time to initiation of systemic antifungal        | 2.0 ± 1.3 days    | 2.3 ± 1.6 days      | 0.88 (0.75 to 1.04)    | 0.13   |                        |        |

\* n/N (%) or mean ± standard deviation shown; \*\*Only significant ( $P < 0.05$ ) and selected non-significant variables on univariate analysis are shown; †Only significant variables on multivariate analysis are shown; ††Adjusted for other variables in the model. CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; TPN = total parenteral nutrition.

TEŞEKÜRLER