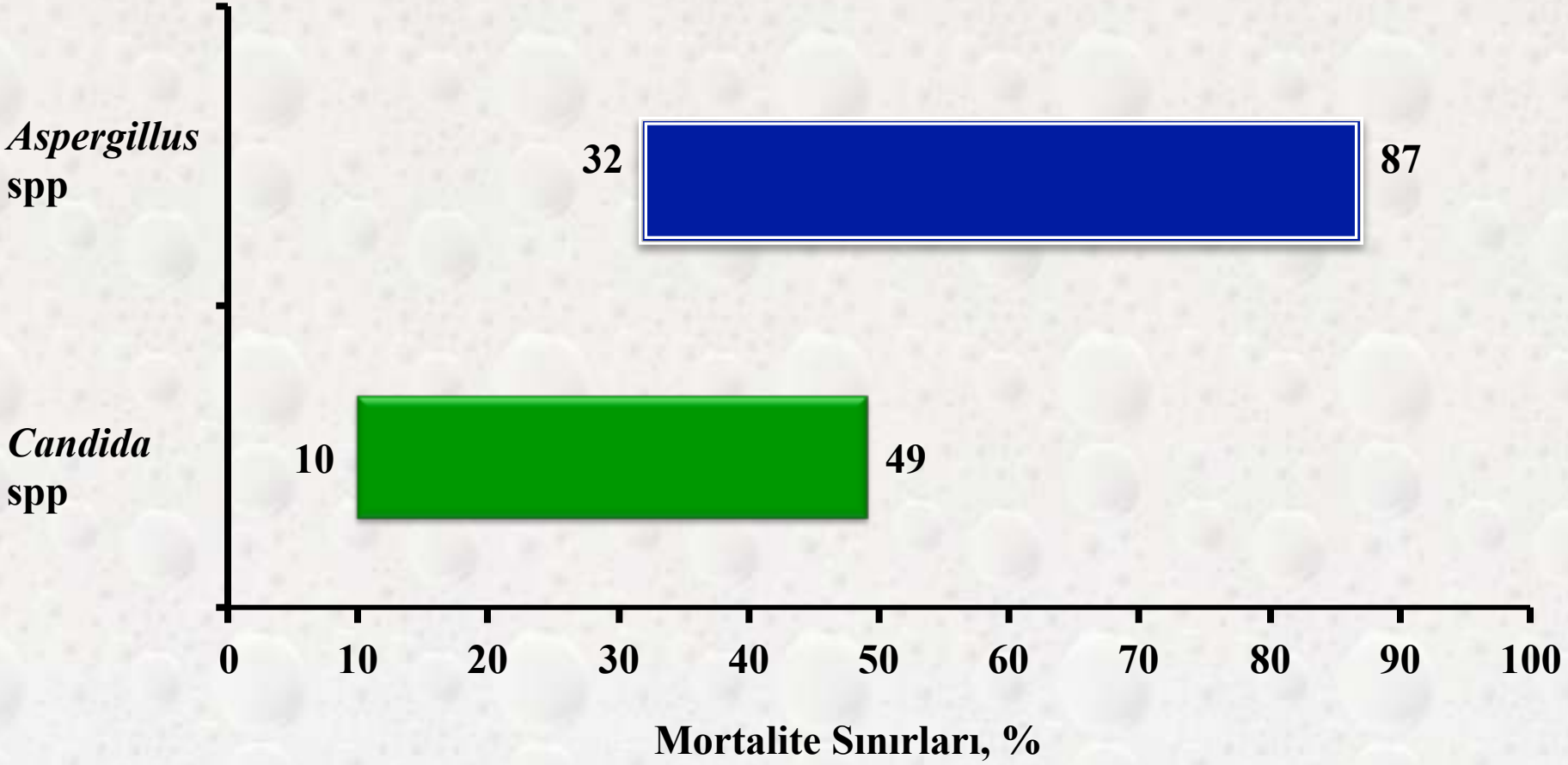
# AMPİRİK VE PREMPTİF ANTİFUNGAL TEDAVİ

**Prof. Dr. Esin ŞENOL**

**Gazi Üniversitesi Tıp Fakültesi**
**Enfeksiyon Hastalıkları ve Klinik Bakteriyoloji Anabilim Dalı**

# YÜKSEK RİSKLİ HASTALARDA MORTALİTE




*Cornely O, et al. Infection 2008;36:296.*

# GÖREVİMİZ TEHLİKE!

**1-2 cm / 24 saat**


Erken tanı
Erken tedavi
İmmun Fonksiyonların düzelmesi

# ANTİFUNGAL TEDAVİDE YOL HARİTAS

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REVIEW ARTICLE

# A practical critique of antifungal treatment guidelines for haemato-oncologists

**AGREE**

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**APPRAİSAL OF GUİDELİNES RESEARCH AND EVALUATİON**

Abstract

## AGREE assessment

With the AGREE Instrument it was possible to objectively assess the guidelines. The assessment highlighted that each guideline differs in objectives, methodology and scope, robustness of findings and recommendations, and sponsorship. Final rankings using this method are shown in Table 1.

Overall, five guidelines are strongly recommended by the working group following the AGREE assessment: the Infectious Diseases Society of America (IDSA) guidelines (Walsh et al., 2008; Pappas et al., 2009), the German Society of Hematology and Oncology (DGHO) guideline on prophylaxis (Cornely et al., 2009), the Australian Society for Infection Diseases (ASID) guidelines (Morrissey et al., 2008; Slavin, 2008; Slavin et al., 2008; Worth et al., 2008; Thursky et al., 2008) and the European Conference on Infections in Leukemia (ECIL-3) guidelines (Maertens et al., 2010).

Table 1. Summary of results from the AGREE assessment of antifungal treatment guidelines.

| Guideline | Area 1 Scope and purpose | Area 2 Stakeholder involvement | Area 3 Rigour of development | Area 4 Clarity and presentation | Area 5 Applicability | Area 6 Editorial independence | Total Scores | Rating |
|---|---|---|---|---|---|---|---|---|
| IDSA (2008) (Walsh et al., 2008) | 78% | 50% | 67% | 89% | 33% | 100% | 68% | Strongly recommended |
| IDSA (2009) (Pappas et al., 2009) | 100% | 17% | 48% | 89% | 11% | 100% | 57% | Strongly recommended |
| ASID (2008)[a] (Slavin, 2008) | 100% | 29% | 69% | 94% | 50% | 92% | 70% | Strongly recommended |
| BCSH (2008) (Prentice et al., 2008) | 33% | 50% | 52% | 33% | 67% | 67% | 48% | Recommend (with provisos) |
| DGHO (2009) (Cornely et al., 2009) | 94% | 42% | 71% | 49% | 0% | 83% | 58% | Strongly recommended |
| DGHO (2009) (Böhme et al., 2009) | 61% | 29% | 60% | 44% | 11% | 25% | 44% | Recommend (with provisos) |
| ECIL-3 (2010) (Maertens et al., 2010) | 89% | 33% | 79% | 67% | 0% | 75% | 61% | Strongly recommended |
| ECIL-3 (2010) (Viscoli et al., 2010) | 83% | 21% | 50% | 39% | 0% | 0% | 38% | Recommend (with provisos) |
| ECIL-3 (2010) (Marchetti et al., 2010) | 89% | 21% | 62% | 39% | 0% | 0% | 43% | Recommend (with provisos) |
| ECIL-3 (2010) (Bretagne et al., 2010) | 83% | 21% | 33% | 44% | 0% | 0% | 35% | Use not recommended |

[a]Note: "Slavin, 2008" contains the relevant information pertaining to the scope, purpose, stakeholder involvement, rigour of guidelines development, clarity and presentation, applicability and editorial independence of all the Australian and New Zealand consensus guidelines (Slavin et al., 2008; Thursky et al., 2008; Worth et al., 2008; Morrissey et al., 2008); for this reason these guidelines have been assessed collectively.

# ANTİFUNGAL BAŞLAMA KARARI

- IFI RİSKİ YÜKSEK
- IFI DÜŞÜNDÜREN KLİNİK

  BULGULAR:Ac,Sinüs;SSS;Karın,Cilt
- GM/β-GLUKAN /SINUS,AC BT BULGULARI
- KLİNİK KÖTÜ:CİDDİ SEPSİS/SEPTİK ŞOK

Table 1 | Risk factors for the development of invasive fungal infection (IFI)

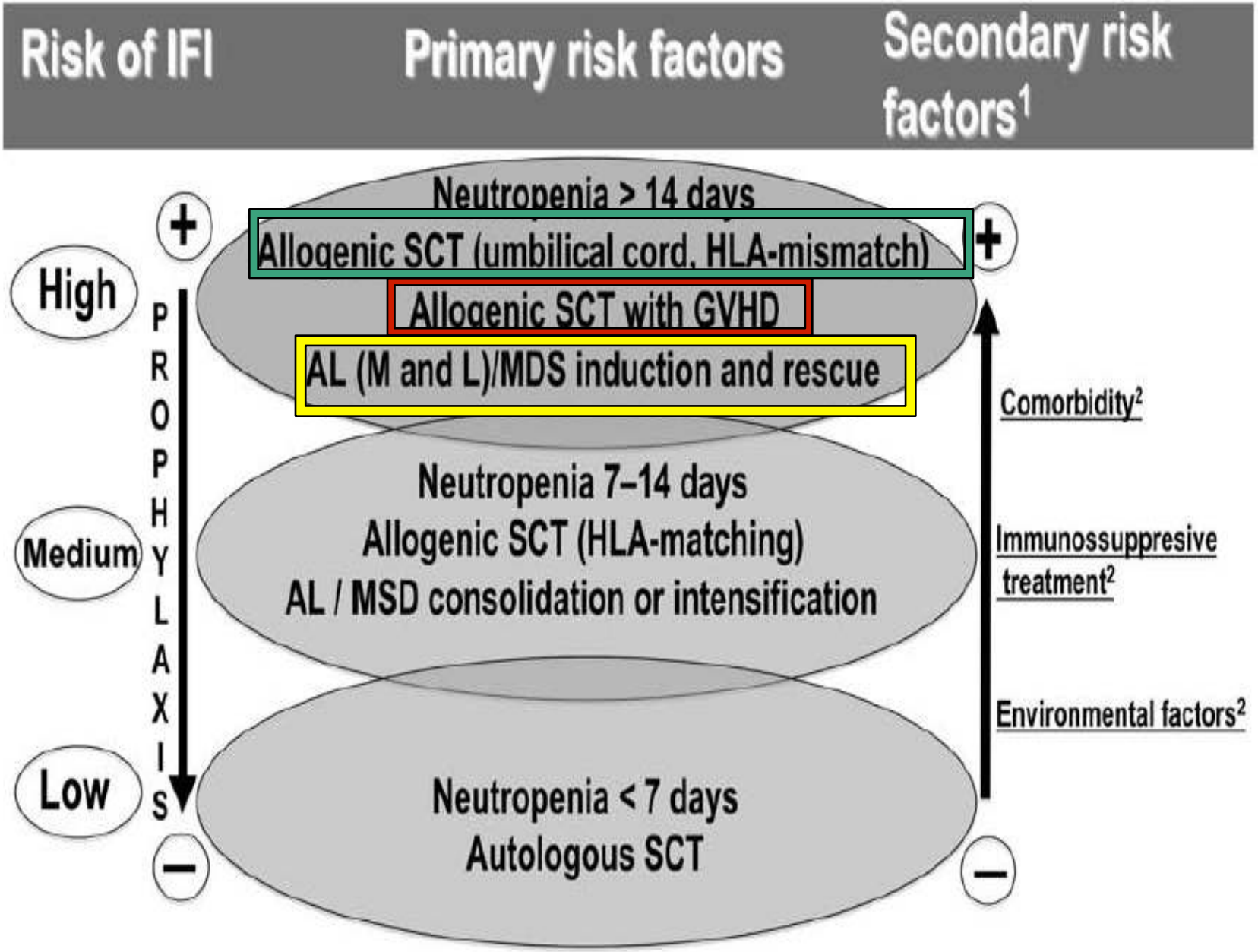
| Neutropenia / lymphopenia | Individual predisposing conditions | Probability of infection / colonization |
|---|---|---|
| **High-risk:** | **Genetic deficiency of innate immune status:** | Absence of HEPA filter |
| Neutropenia of < 100/mm3 and > 14 days | MBL | Local prevalence of IFI |
| Lymphopenia/functional impairment of lymphocytes | TLR4-2 | History of IFI |
| • Prolonged treatment with corticosteroids | Dectin-1 | Underlying lung diseases |
| • Anti-TNF, ATG | Plasminogen | |
| • Alemtuzumab | IL-10 | |
| • CMV infection | Pulmonary surfactant | |
| **Medium-risk:** | **Iron overload** | |
| Neutropenia 7-14 days | **Comorbidity:** | |
| **Low-risk:** | Sustained hyperglycemia | |
| Neutropenia < 7 days | Metabolic acidosis | |
| | Structural pulmonary disease | |

NÖTROPENİ

LENFOPENİ

TNF: tumor necrosis factor; ATG: anti-thymocyte globulin; MBL: mannan-binding lectin; TLR: toll-like receptors; IL: interleukin; HEPA: high efficiency particulate air.

Rev Esp Quimioter 2011;24(3):117-122


Risk of IFI
Primary risk factors
Secondary risk factors[1]
High
Medium
Low
+
–
PROPHYLAXIS
Neutropenia > 14 days
Allogenic SCT (umbilical cord, HLA-mismatch)
Allogenic SCT with GVHD
AL (M and L)/MDS induction and rescue
Neutropenia 7–14 days
Allogenic SCT (HLA-matching)
AL / MSD consolidation or intensification
Neutropenia < 7 days
Autologous SCT
+
–
Comorbidity[2]
Immunossuppresive treatment[2]
Environmental factors[2]

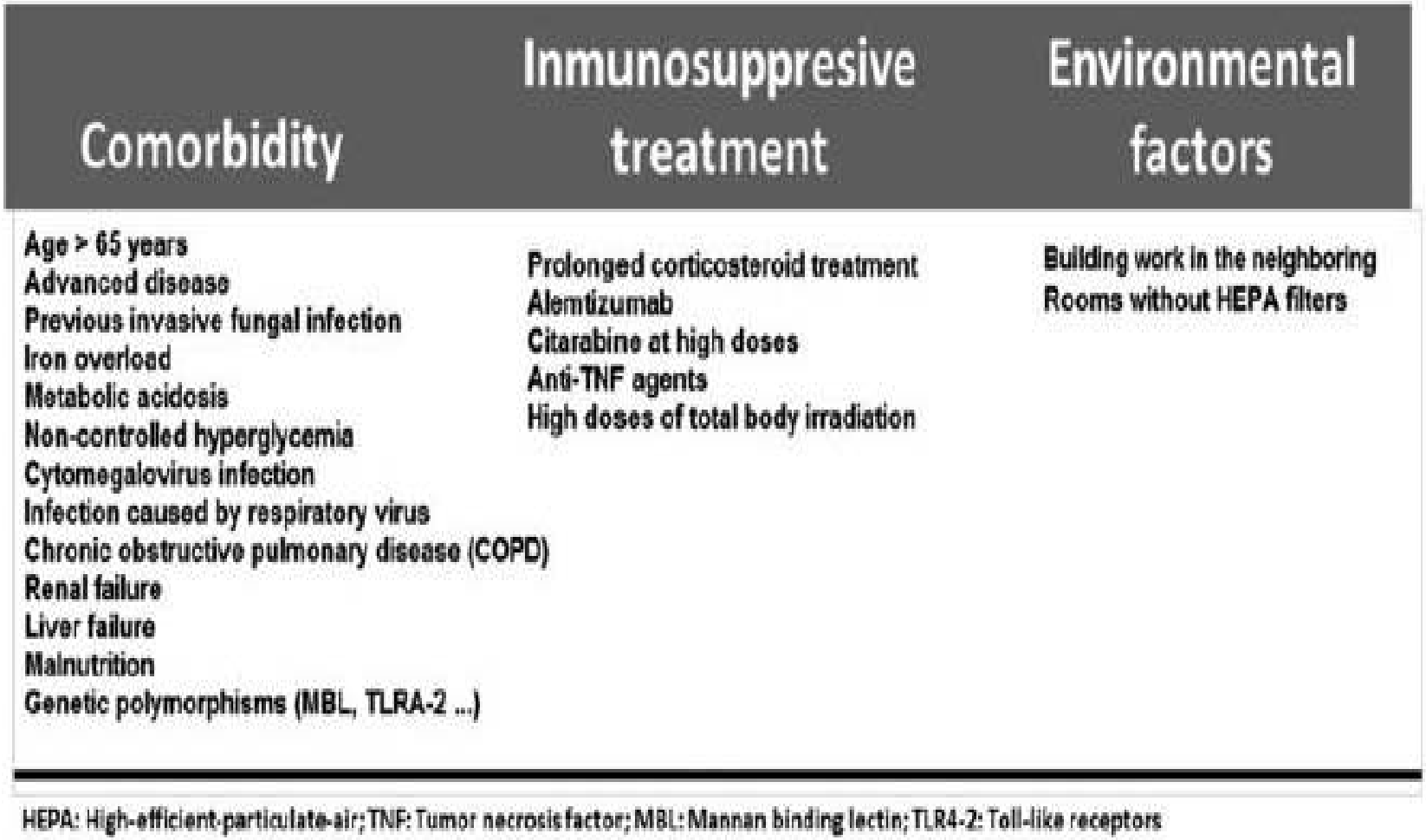



Figure 2 | Secondary risk factors of invasive fungal infection

# IFH Tedavi Stratejileri

## Hedeflenmiş Tedavi

**KANITLANMIŞ- IFI TANISI: Steril Sıvılar/DOKU**
**TÜM OLGULARIN <%2**

## Empirik Tedavi

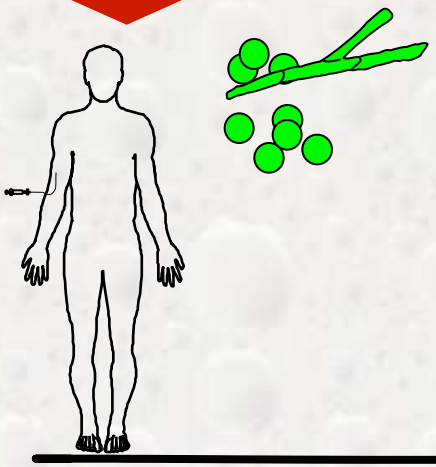
**Yüksek Risk + PFUO + Marker Ø**

## Preemptif Tedavi

**Yüksek Riskli Hasta + ASemptomatik + GM/B-Glukan / CT (EORTC/MSG -Poss/Prob)**

# IFI Tedavi Stratejileri

- ✓ Yüksek riskli Hasta
- ✓ Yüksek riskli dönem



ATEŞ;
yüksek riskli-
3-5.gün
Orta riskli::5-7
gün

Hastalık yükü

Kaba mortalite
60% to 90%

İNFEKSİYON ODAĞI/YÜKSEK OLASI

TANISAL TETİKLENMİŞ
EAFT
+CT/
GM
POZİTİF
KÜLTÜR

Hastalık yok | Sinus/Ac.B | dite/

Profilaksi | Pre-emp | rtalite

*Perfect et al. Oncology 2004;18:5-14.*

# HEMATOLOJİK MALİNİTELERDE- ANTİFUNGAL TEDAVİ

## 2 küçük çalışma:

- 30 hasta, 7. gün ateş
- Antibiyotik tedavisine antifungal eklemek fungal infeksiyonları azalttı
- Amfo-B vs kontrol
- Antibiyotik tedavisinin 4. gününde ateş
- Fungal ölümler ve IFI azaldı

*Pizzo. Am J Med 1982;72;101-111*
*EORTC. Am J Med 1989;86;668-675*

**1980-2000 AMPİRİK ANTİFUNGAL TEDAVİ "ALTIN STANDART"**

| Possible Causes of Fever | Approximate Frequency in High-Risk Patients (%) |
|---|---|
| Fungal infections susceptible to empirical therapy | 40 |
| Fungal infections resistant to empirical antifungal therapy | 5 |
| Bacterial infections (with cryptic foci and resistant organisms) | 10 |
| *Toxoplasma gondii*, mycobacteria, or fastidious pathogens (legionella, mycoplasma, *Chlamydia pneumoniae*, bartonella) | 5 |
| Viral infections (herpesviruses, cytomegalovirus, Epstein–Barr virus, human herpesvirus 6, varicella–zoster virus, herpes simplex virus) and respiratory pathogens such as parainfluenza virus, respiratory syncytial virus, influenzaviruses | 5 |
| Graft-versus-host disease after hematopoietic stem-cell transplantation | 10 |
| Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens) | 25 |

*Corey & Boeckh. N Engl J Med 2002*

# 2. Difficulties in diagnosis

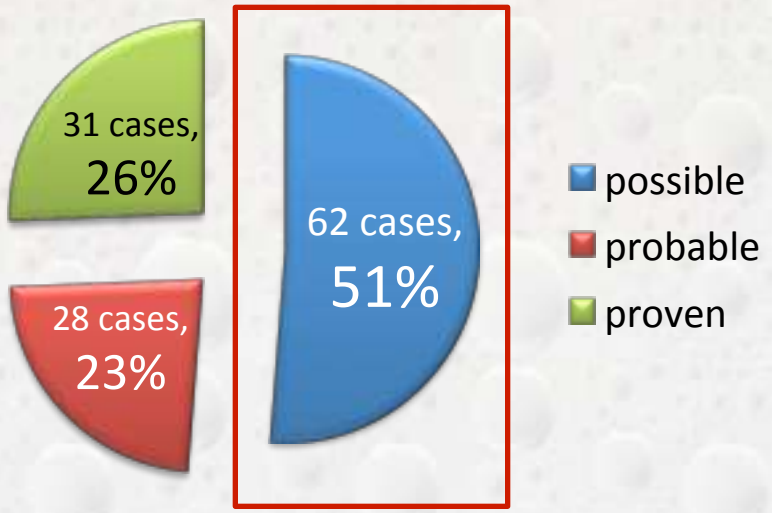
- 19 Italian Hematological Centers (2007-09)
  - 3197 NEWLY DIAGNOSED patients

**869 FEBRILE EVENTS**

| | EVT | % |
|---|---|---|
| Bacterial | 301 | 34.6 |
| Fungal | 95 | 10.9 |
| Viral | 7 | 0.8 |
| DTRF | 48 | 5.5 |
| FUO | 386 | 44.4 |
| Mixed infections | 32 | 3.6 |
| TOTAL | 869 | |

**44% FUO**

**51% possible**




*Pagano et al, Ann Hematol 2012*

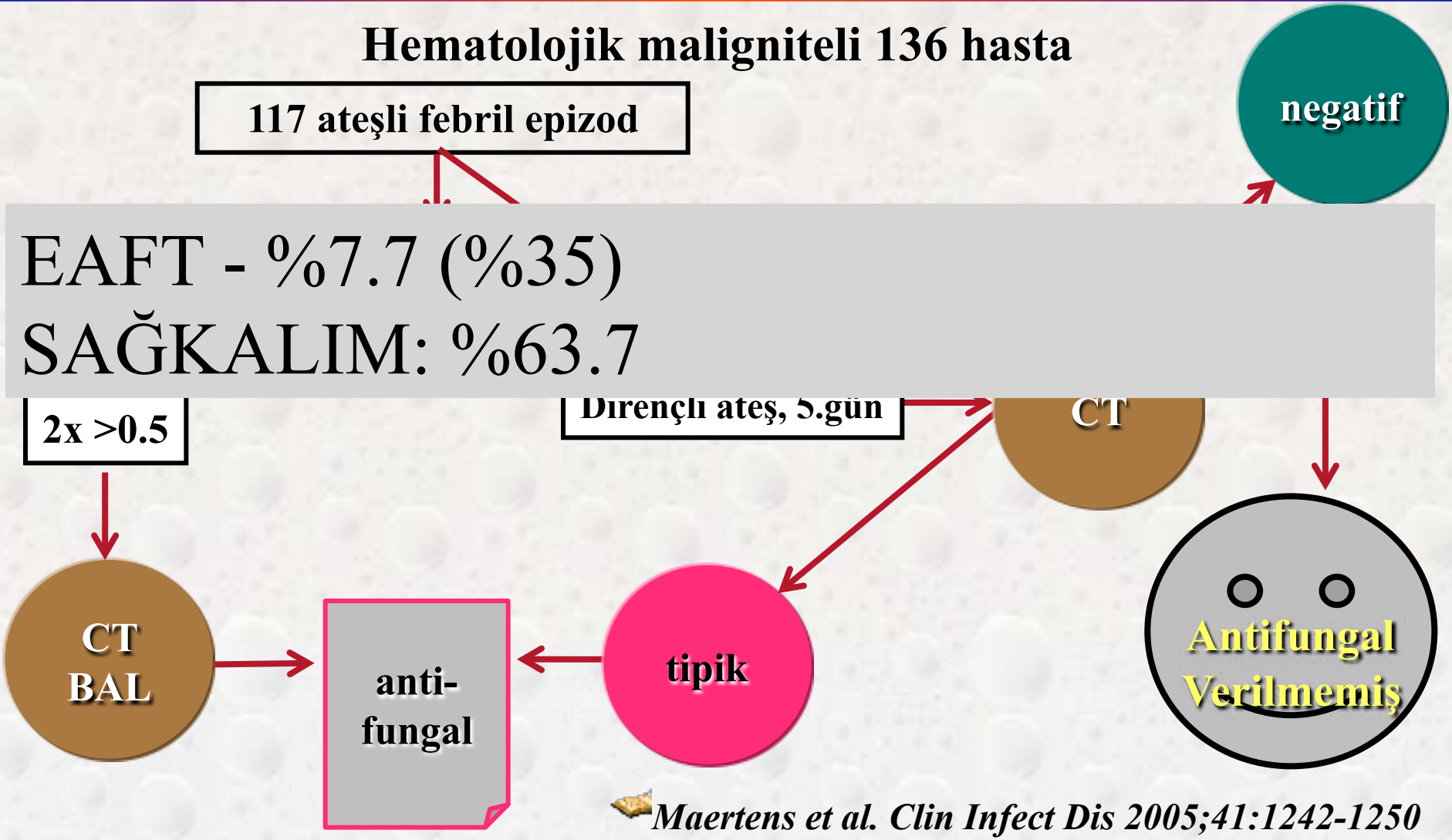
# Ampirik Antifungal Tedavi?

- 1.8 IFI tedavi etmek için :100 hasta
- AFT ilişki mortalite %5-15
- Toksisite ve maliyet
- Bazal infeksiyon tedavisi ort: 22-23 gün
- Sadece ateş tedavisi ort: 16-18 gün

# Ampirik Antifungal Tedavi - Gelişmeler

- Risk Grupları Tanımlamaları
- Yeni Tanı Yöntemleri (GM, β-D glukan, BT)
- Daha Emniyetli Ajanlar
- Seçilmiş Hasta Gruplarında Hedeflenmiş Tedaviler

# GALACTOMANAN AND CT-SCAN-GUIDED EARLY TREATMENT OF INVASIVE ASPERGILLOSIS




*Maertens et al. Clin Infect Dis 2005;41:1242-1250*

## Table 2 Empirical versus preemptive antifungal therapy

| Empirical treatment | Preemptive treatment |
|---|---|
| Earliness | Initiation 3-4 days after empirical therapy |
| Lower probability of poor clinical evolution and death | Higher probability of poor clinical evolution or death |
| Overtreatment | Fewer unnecessary treatments |
| Higher health care costs | Complex logistic process |

# Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Françoise Foulet,[2] Mathieu Kuentz,[1] Patrick Maison,[3] Stéphane Bretagne,[2] and Michaël Schwarzinger[9,10]

- **Yüksek Riskli Hastalar; AML –indüksiyon/ konsolidasyon, OTO-KHN**
- **2 Tedavi Stratejisi - 2. hf sağkalım (non-inferiorite; %90 sağkalım, <%10 mort. farkı, sınır - %8)AFT; Amfo-B, L-AmB**
- **Ampirik; ATEŞ**
- **Pre-emptif: 4. gün ateş+ Klinik , Radyolojik , Mikolojik kriter; GM ≥1.5,**

*Clin Infect Dis 2009;48:1042-51.*

# Sonuçlar

**Table 2. Efficacy end points in the intention-to-treat population ($n$ = 293).**

| Efficacy end point | Empirical treatment arm (n = 150) | Preemptive treatment arm (n = 143) | Difference (95% CI) | P* |
|---|---|---|---|---|
| Primary | | | | |
| Alive at study completion | 146 (97.3) | 136 (95.1) | 2.2 (−5.9 to 1.4) | .31 |
| Secondary | | | | |
| IFI | 4 (2.7) | 13 (9.1) | −6.4 (−10.9 to −1.9) | <.02 |
| Duration of temperature >38°C,[b] days | | | | |
| Median (IQR) | 13 (5–21) | 12 (5–20) | ... | NS |
| Range | 1–72 | 1–59 | ... | |

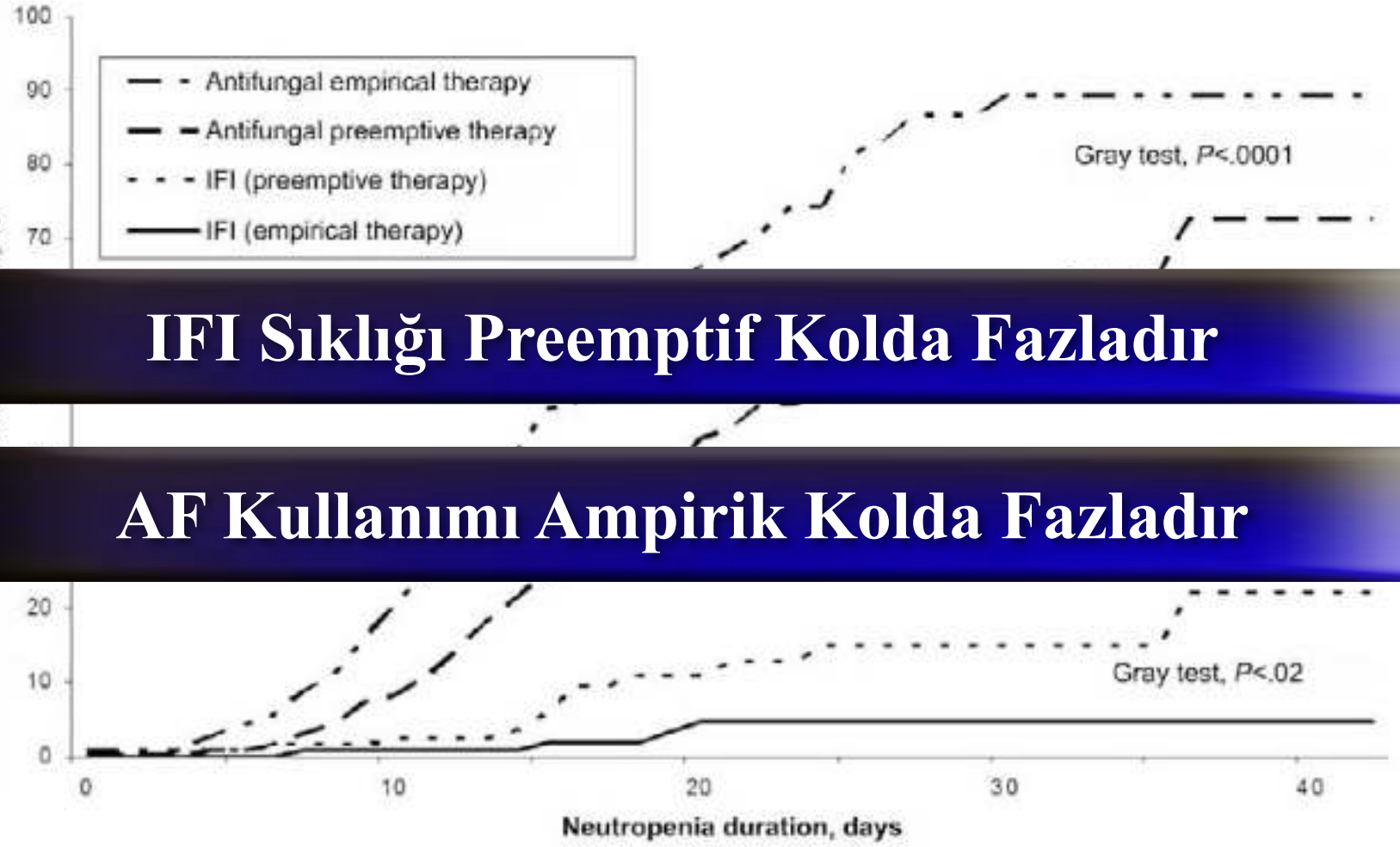
**NOTE.** Data are no. (%) of patients, unless otherwise indicated. IFI, invasive fungal infection; IQR, interquartile range; NS, not significant.

[a] By Cochran-Mantel-Haenszel test for qualitative variables; by Wilcoxon sum-rank test for skewed quantitative variables.

[b] Excludes 14 patients without fever (8 in the empirical treatment group and 6 in the preemptive treatment group).

**Yüksek Riskli Hematolojik Malinitelerde Pre-emptif ve Ampirik Tedavi Mortalitesi Farksız**

*Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.*




**IFI Sıklığı Preemptif Kolda Fazladır**

**AF Kullanımı Ampirik Kolda Fazladır**

**Figure 2.** Cumulative incidence of antifungal therapy and invasive fungal infection (IFI) during neutropenia ($n = 287$)

*Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.*

**Table 3. Antifungal therapy in the intention-to-treat population ($n$ = 293).**

| End point | Empirical treatment group | Preemptive treatment group | $P^a$ |
|---|---|---|---|
| Antifungal treatment | 92/150 (61.3) | 50/143 (35.0) | <.001 |
| Reason for starting antifungal treatment[b] | | | |
| Isolated fever between day 4 and day 14 after antibacterial treatment initiation | 55 (59.8) | 1 (1.8) | <.001[c] |
| Pneumonia | 6 (6.5) | 25 (46.4) | |
| Severe mucositis | 8 (8.7) | 10 (17.9) | |
| Isolated fever beyond day 14 | 11 (12.0) | 7 (12.5) | |
| Septic shock | 5 (5.4) | 3 (5.4) | |
| Positive result of galactomannan antigen test | 2 (2.2) | 3 (5.4) | |
| High-cost antifungal agents (liposomal AmB, caspofungin, or voriconazole) | 3.7 ± 7.6 | 2.6 ± 5.8 | NS |
| Range | 0–21,727 | 0–15,388 | |
| Length of hospital stay, days | | | |
| Mean ± SD | 30.3 ± 10.5 | 30.5 ± 10.2 | |
| Range | 11–100 | 14–80 | NS |

**NOTE.** Data are no. or proportion (%) of patients, unless otherwise indicated. AmB, amphotericin B; IQR, interquartile range; NS, not significant.

[a] By $\chi^2$ test or Fisher's exact test for qualitative variables; by Wilcoxon rank sum test for skewed quantitative variables.

[b] Estimates were computed for patients who received antifungal treatment: 92 patients in the empirical treatment group and 50 patients in the preemptive treatment group.

[c] By $\chi^2$ test comparing isolated fever before day 14 with other situation.

**En Sık Tedavi Nedeni; Pre-emptif - Pnömoni, Ampirik - Ateş**

**AFT - preemptif grupta 1 hafta geç başlanıp, daha kısa süre kullanılıyor, bu da maliyeti azaltıyor....**

*Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.*

**Table 4. Subgroup analysis of patients receiving consolidation therapy or stem cell transplantation compared with patients receiving induction therapy, in the intention-to-treat population ($n$ = 293).**

| End point | Consolidation therapy or transplantation | | | Induction therapy | | |
|---|---|---|---|---|---|---|
| | Empirical treatment group (n = 72) | Preemptive treatment group (n = 70) | P* or difference (95% CI) in all-cause outcomes | Empirical treatment group (n = 78) | Preemptive treatment group (n = 73) | P* or difference (95% CI) in efficacy outcomes |
| Duration of neutrophil count <500 neutrophils/μm³,† days | | | | | | |
| Median (IQR) | 11 (8–16) | 12 (10–15) | NS | 26 (21–30) | 26 (18–32) | NS |
| Range | 6–41 | 8–30 | | 9–60 | 5–57 | |
| Alive at study completion | 72 (100) | 68 (97.1) | 2.9 (−6.1 to 0.4) | 74 (94.9) | 68 (93.2) | 1.7 (−5.0 to 4.8) |
| Invasive fungal infection | | | | | | |
| All | 1 (1.4) | 1 (1.4) | 0 (−3.3 to 3.3) | 3 (3.8) | 12 (16.4) | −12.6 (−22.6 to −4.8) |
| Due to Aspergillus species | 1 (1.4) | 1 (1.4) | NS | 3 (3.8) | 7 (9.6) | NS |
| Due to Candida species | 0 (0) | 0 (0) | NS | 0 (0) | 5 (6.8) | <.05 |
| Antifungal prophylaxis | 40 (55.6) | 40 (57.1) | NS | 23 (29.5) | 29 (39.7) | NS |
| Antifungal treatment | 20 (28.9) | 13 (18.6) | <.01 | 64 (82.1) | 43 (58.9) | <.01 |
| Duration of fever before antifungal treatment, median days (IQR) | 6 (4–8) | 6 (3–12) | NS | 9 (3–14) | 14 (9–16) | <.05 |
| Change in creatinine clearance (at end of study minus at baseline), mean ± SD | −3.4 ± 19.5 | −3.6 ± 19.3 | NS | −19.7 ± 25.4‡ | −7.8 ± 35.0 | <.05 |
| Total costs of antifungal drugs, 2005 € | | | | | | |
| Mean ± SD | 1775 ± 2615 | 377 ± 1379 | <.02 | 3245 ± 1832 | 2528 ± 1230 | <.05 |
| Range | 0–11,122 | 0–7500 | | 0–20,726 | 0–16,500 | |
| Length of hospital stay, mean ± SD, days | 26.4 ± 6.3 | 26.4 ± 7.4 | NS | 34.8 ± 11.5 | 35.0 ± 10.3 | NS |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; NS, not significant.

* By $\chi^2$ test or Fisher's exact test for qualitative variables; by Wilcoxon rank-sum test for skewed quantitative variables.

† Excludes 6 patients without neutropenia (4 in the empirical treatment group—including 1 in the autologous stem cell transplant subgroup, 1 in consolidation therapy subgroup, and 2 in the induction therapy subgroup—and 2 in the preemptive treatment group, both of whom were in the induction therapy subgroup).

‡ $P$ < .001 by the paired $t$ test comparing changes in creatinine clearance from baseline to study completion.

*Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.*

# The use and efficacy of empirical *versus* pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project

Livio Pagano,[1] Morena Caira,[1] Annamaria Nosari,[2] Chiara Cattaneo,[3] Rosa Fanci,[4] Alessandro Bonini,[5] Nicola Vianelli,[6] Maria Grazia Garzia,[7] Mario Mancinelli,[1] Maria Elena Tosti,[8] Mario Tumbarello,[9] Pierluigi Viale,[10] Franco Aversa,[11] and Giuseppe Rossi[12] on behalf of the HEMA e-Chart Group, Italy

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## ABSTRACT

### Background

Neutropenic patients with persistent fever despite antibiotic therapy are managed with empirical or pre-emptive antifungal therapy. The aim of the present study was to evaluate the current clinical use and efficacy of these two approaches in patients with high risk hematologic conditions.

### Design and Methods

An electronic medical record system, the "Hema e-Chart", was designed and implemented to collect information prospectively on infectious complications, particularly on invasive fungal diseases, in patients with hematologic malignancies treated with chemotherapy and/or autologous or allogeneic hemopoietic stem cell transplantation. The patients were enrolled from Hematology units distributed widely across Italy.

### Results

Three hundred and ninety-seven adults with hematologic malignancies treated with chemotherapy with persistent fever and suspected invasive fungal disease were evaluable for the study (190 treated had been treated with empirical antifungal therapy and 207 with pre-emptive antifungal therapy). There was a significantly lower incidence of proven/probable invasive fungal diseases in patients treated with empirical antifungal therapy (n=14, 7.4%) than in patients treated with pre-emptive therapy (n=49, 23.7%) ($P<0.001$). The rate of deaths attributable to invasive fungal diseases was significantly lower in subjects treated with empirical antifungal therapy (1 case; 7.1%) than in subjects treated with pre-emptive therapy (11 cases; 22.5%) ($P=0.002$).

### Conclusions

These data indicate that empirical antifungal treatment decreased the incidence of invasive fungal disease and of attributable mortality with respect to a pre-emptive antifungal approach in neutropenic febrile patients with hematologic malignancies. *(ClinicalTrials.gov Identifier: NCT01069887)*

Key words: empirical antifungal therapy, pre-emptive antifungal therapy, hematologic malignancies.

*Citation: Pagano L, Caira M, Nosari A, Cattaneo C, Fanci R, Bonini A, Vianelli N, Garzia MG, Mancinelli M, Tosti ME, Tumbarello M, Viale P, Aversa F, and Rossi G on behalf of the HEMA e-CHART Group, Italy. The use and efficacy of empirical versus pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project. Haematologica 2011;96(9):1366-1370. doi:10.3324/haematol.2011.043588*



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Table 1. Comparison between empirical and pre-emptive treatment groups: principal demographic characteristics and clinical outcomes in 397 registered patients.

| Variable | Empirical n=190 (%) | Pre-emptive n=207 (%) | P value |
|---|---|---|---|
| Age, years (range) | 52.3 (14-83) | 58.1 (18-84) | <0.001 |
| Chronic lymphocytic leukemia | 2 (1.1) | 1 (0.5) | 0.51 |
| Hodgkin's lymphoma | 2 (1.1) | 1 (0.5) | 0.51 |
| Prophylaxis (%) | 93 (48.9) | 121 (58.5) | 0.05 |
| Kind of prophylaxis, n. (%) | | | |
| Itraconazole | 48 (51.6) | 60 (49.6) | 0.48 |
| Fluconazole | 36 (38.7) | 47 (38.8) | 0.35 |
| Posaconazole | 7 (7.5) | 9 (7.4) | 0.73 |
| Other | 2 (1) | 5 (2.4) | 0.30 |
| Prophylaxis duration, mean days (SD) | 8.3 (8.2) | 8.3 (6.6) | 0.9 |
| Others | 5 (2.6) | 7 (2.4) | 0.86 |
| IFD-attributable mortality (%) | 1/14 (7.1) | 11/49 (22.5) | 0.002 |
| Overall 90-day mortality (%) | 12/190 (6.3) | 33/207 (15.9) | 0.002 |

SD: standard deviation, IFD: invasive fungal disease, 1 Histoplasmosis, 2 Aspergillus spp., 3 Candida spp., 4 Rhizopus spp.

**IFI-mort; ampirik ve pre-emptif; %7.1 ve %22.5; p: 0.002**

**IFI insidansı ampirik kolda düşüktür (%23.7 ve %14.7, p<0.001)**

*Pagano L, et al. Haematologica 2011;96(9):1366-70.*

Table 2. Predictors of mortality in the 397 registered patients.

| Variable | N. (%)of patients Dead (n=45) | Survivors (n=352) | *P* value | OR (95% CI) |
|---|---|---|---|---|
| **Univariate analysis** | | | | |
| Demographic information | | | | |
| Male sex | 29 (64.4) | 200 (56.8) | 0.32 | 1.37 (0.69-2.81) |
| Age (year [mean SD]) | 62±10 | 54±16 | <0.001 | |
| Hematologic malignancy | | | | |
| Acute myeloid leukemia | 34 (75.5) | 287 (81.5) | 0.33 | 0.70 (0.32-1.61) |
| Chronic myeloid leukemia | 0 | 2 (0.6) | 1 | 0 (0-15.25) |
| Acute lymphocytic leukemia | 4 (8.9) | 21 (5.9) | 0.50 | 1.53 (0.36-4.87) |
| Chronic lymphocytic leukemia | 1 (2.2) | 2 (0.6) | 0.30 | 3.97 (0.06-77.42) |
| Non-Hodgkin's lymphoma | 6 (13.3) | 24 (6.8) | 0.13 | 2.10 (0.66-5.70) |
| Hodgkin's lymphoma | 0 | 3 (0.8) | 1 | 0 (0-10.16) |
| Multiple myeloma | 0 | 6 (1.7) | 1 | 0 (0-5.03) |
| Myelodysplastic syndromes | 0 | 7 (1.9) | 1 | 0 (0-4.29) |
| Clinical presentation | | | | |
| Central venous catheter | 21 (46.7) | 180 (51.1) | 0.57 | 0.83 (0.42-1.63) |
| Neutropenia (PMN<0.5×10⁹/L) | 40 (88.9) | 326 (92.6) | 0.38 | 0.63 (0.22-2.25) |
| Antifungal prophylaxis | 20 (44.4) | 194 (55.1) | 0.17 | 0.65 (0.33-1.27) |
| Steroid use | 6 (13.3) | 27 (7.6) | 0.19 | 1.85 (0.58-4.95) |
| Positive lung X-ray | 15 (33.3) | 82 (23.3) | 0.14 | 1.64 (0.78-3.33) |
| Positive lung CT-scan | 24 (53.3) | 162 (46) | 0.35 | 1.24 (0.68-2.63) |
| Etiology and treatment | | | | |
| Yeast | 4 (8.9) | 15 (4.3) | 0.17 | 2.19 (0.50-7.31) |
| Molds | 8 (17.8) | 36 (10.2) | 0.13 | 1.89 (0.71-4.55) |
| Empirical antifungal treatment | 12 (26.7) | 178 (50.6) | 0.002 | 0.35 (0.16-0.73) |
| **Multivariate analysis** | | | | |
| Age (year [mean SD]) | | | 0.006 | 1.03 (1.01-1.06) |
| Empirical antifungal treatment | | | 0.01 | 0.40 (0.20-0.82) |

*SD: standard deviation; OR: odd's ratio; PMN: polymorphonuclear cells.*

*Pagano L, et al. Haematologica 2011;96(9):1366-70.*

- **2 çalışmadaki pre-emptif tedavi tanımı**
- **“Something More” than persistent fever**

*Castagnola E, Haupt R. Editorial, Hematol 2011*

# Pre-emptive strategy criteria

## *Data from literature*

| Reference | Intensive work-up | Criteria to start pre-emptive |
|---|---|---|
| **Maertens *et al*, 2005** | - Cultures of blood, sputum and infected sites<br>- Chest CT<br>- Bronchoscopy with BAL | - GM ≥ 0.5 x 2; or<br>- Pos for both TAC and BAL |
| **Oshima *et al*, 2007** | Not specified | - Fever ≥ 7 days + GM ≥ 0.6 x 2; or<br>- Pos Rx +/- TAC |
| **Cordonnier *et al*, 2009** | - Blood cultures x 2, urine culture<br>- X-ray | - Fever ≥ 4 days + GM ≥ 1.5 x 1; or<br>- Clinical suspicion of IFD |
| **Dignan *et al*, 2009** | - Blood cultures x 2, X-ray<br>- Chest CT | - Fever ≥ 3 days + pos TAC; or<br>- Clinical suspicion of IFD |
| **Aguilar-Guisado *et al*, 2010** | - Blood cultures, X-ray<br>- Chest CT | - Fever ≥ 5 days + sever sepsis, septic shock, infection of lung, skin CNS, sinus, abdomen |
| **Girmenia *et al*, 2010** | - Blood cultures x 3, GM x 3, CT | Fever ≥ 4 days + proven/probable/ possible IFD |
| **Tan *et al*, 2011** | - GM x 2 | -fever + GM ≥ 0.5 x 2; or<br>-fever + GM ≥ 0.5 + pos CT |

# Ampirik Antifungal Tedavi: Meta-analiz

- 1996-2003: Tanı olmayan persistan ateşler, RKÇ: 30 çalışma, 6303 hasta
- Mortalite: RR: 0.82, 95% CI: 0.5-1.34
- IFI: RR: 0.25, 95% CI: 0.12-0.54
- NNT: 17
- L-AmB vs diğer lipid bileşikler, L-AmB mortalite ve IFI riskini anlamlı azaltıyor; RR: 1.57, RR: 1.48
- Caspofungin ve L-AmB en az yan etki

*Goldberg E. Eur J Cancer 2008*

# EMPİRİK VE PREMPTİF TEDAVİ: GÖRÜŞLER

Livio Pagano

V. INTERNATIONAL EURASIAN HEMATOLOGY CONGRESS
15-19 OCTOBER 2014
MARDAN PALACE HOTEL

patients who need it

Patients who do not need it

| Yes, absolutely | Yes, perhaps | Do not know | Maybe not | No, definitely |
|---|---|---|---|---|

# GERÇEK HAYAT!!!

**En Sık Karşılaşılan Klinik**

**Senaryo: Uzamış Ateş + Özgün Olmayan**

**Klinik Bulgular + Özgün Olmayan**

**Radyolojik Bulgular**

**Pnömoni - Empirik veya Preemptif Tedavi**

**için EORTC/MSG –IFH Tanım Kriterlerine Uymuyor**

Table 1. Patterns of invasive fungal disease in pratice, based on 2008 EORTC-MSG criteria.

| | A | B | C | | | | D | E |
|---|---|---|---|---|---|---|---|---|
| | - | - | I | II | III | IV | - | |
| Radiological signs and clinical symptoms | No | Persistent febrile neutropenia | No | Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria) | | Radiological signs on CT (dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity) | | Not considered necessary |
| Mycology results | Negative | Negative | Positive biomarker or microscopy or culture | Negative | Positive biomarker or microscopy or culture | Negative | Positive biomarker or microscopy or culture | Positive tissue or specimen from a sterile site |
| Clinical evidence of IFD | No | No | No | No | No | Yes | Yes | Yes |
| Mycological evidence of IFI | No | No | Yes | No | Yes | No | Yes | Yes |
| Final diagnosis | Unclassified | | | | | Possible IMD | Probable IMD | Proven IMD |
| Management | Prophylaxis | Empirical therapy | Diagnostic-driven (pre-emptive) therapy | | | | Targeted therapy | |

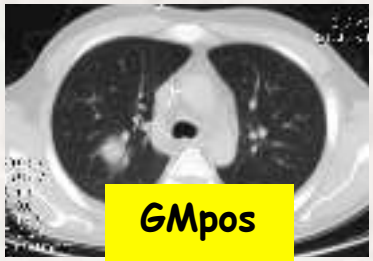
*Maertens JA, et al. Haematologica 2012;97(3):325-7*

## PRE-EMPTIVE

SURVEY

TC

TC




TC

Risk Period

GM GM GM GM GM GM GM GM GM GM GM

*Maertens et al. Clin Infect Dis 2005*

*Girmenia et al. JCO 2009*

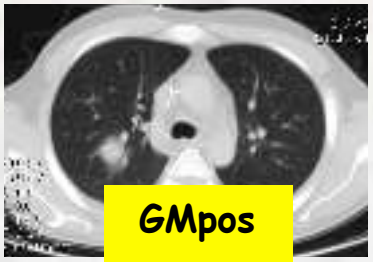
4gg

Fever

GM GM GM

## DIAGNOSTIC-DRIVEN

TC




SYMPTOMATIC APPROACH

*Courtesy of C. Girmenia*

# REHBERLERE UYMAK

## Rehberlerdeki kanıt düzeyleri yeterli mi?

IDSA 44 rehberdeki 4182 önerinin kanıt gücü;

%50'sinin III

%31'inin II

%16'sının I

Clin Infect Dis 2010; 51(10):1147–1156

## Rehberler pratikle uyumlu mu?

Rehberlere esas teşkil eden çalışmalarda yer alan hastalar seçilmiş hastalar!

# Rehbere uymak iyi mi?

IDSA Kandida rehberine uyum, 199 hasta

%76 uyum, ölüm: %24 vs %57 (P: 0.003)

Diagn Microbiol Infect Dis 2005;52:29-34

Kanıtlı veya yüksek olasılıklı IA, 136 akut lösemi hastası

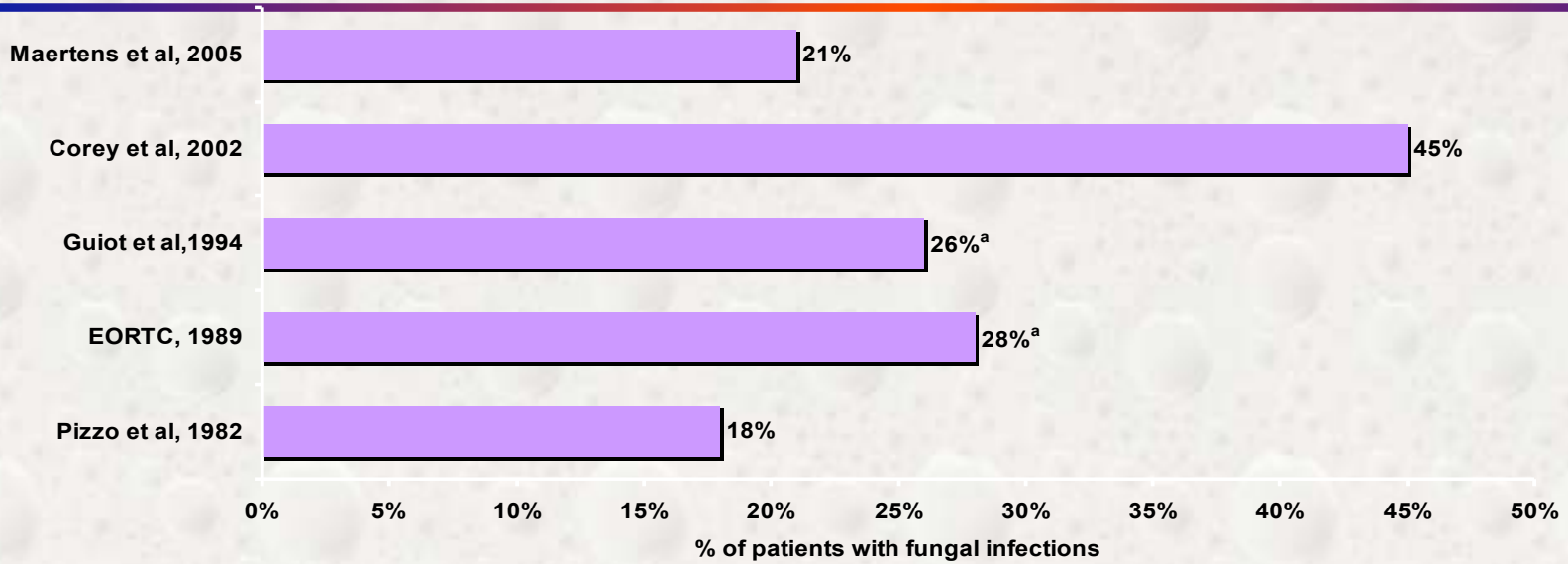
IDSA rehberine uyum: %56 Tedavi başarısı %71 vs %59 (P>0.05)

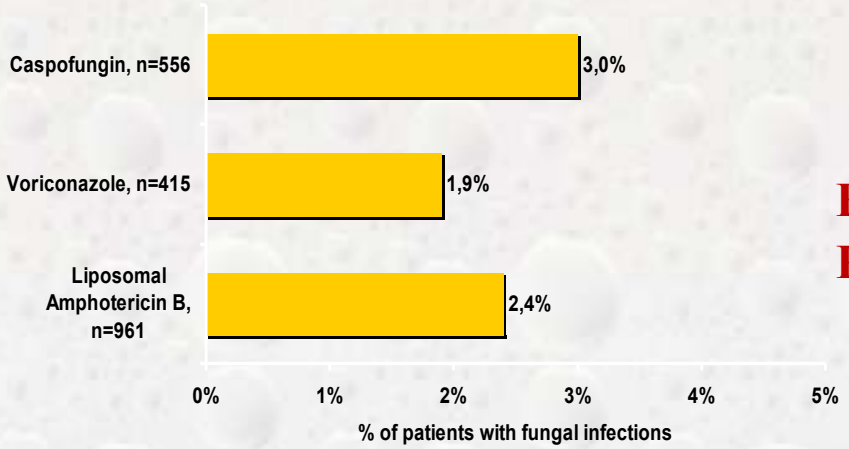
ECIL rehberine uyum:%28 Tedavi başarısı %84 vs %62 (P>0.05)

J Antimicrob Chemother 2010;65:2013-2018

SONUÇ: Antifungal yönetimi, ekip çalışması, eldeki verilere (hasta) rehber penceresinden bakarak klinik karar vermeli!

# EMPIRIK TEDAVI VERILMEYEN IFI'LI HASTALARDA İNVAZIF FUNGAL İNFEKSIYONLAR..




**Empirik tedavi çalışmaları; 3 RKÇ**
**Kanıtlanmış IFI: <6 -%10**

*Klastersky J and Paesmans M, Support Care Cancer 2007;15:137–141*

## VII. What Is the Role of Empirical or Pre-emptive Antifungal Therapy and Which Antifungal Should be Used?

***Recommendations***

*High risk*

28. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days (A-I). Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving anti-mold prophylaxis, but switching to a different class of anti-mold antifungal that is given intravenously should be considered (B-III).

29. Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography (CT) signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi (such as *Candida* or *Aspergillus* species) from any body site may have antifungal agents withheld (B-II). Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified.

*Low Risk*

30. In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended (A-III).

Bone Marrow Transplantation (2011) 46, 709-718

www.nature.com/bmt

ORIGINAL ARTICLE

# European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 Update

J Maertens[1], O Marchetti[2], R Herbrecht[3], OA Cornely[4], U Flückiger[5], P Frère[6], B Gachot[7], WJ Heinz[8],

In 2005, several groups, including the European Group for Blood and Marrow Transplantation, the European Organization for Treatment and Research of Cancer, the European Leukemia Net and the Immunocompromised Host Society created the European Conference on Infections in Leukemia (ECIL). The main goal of ECIL is to elaborate guidelines, or recommendations, for the management of infections in leukemia and stem cell transplant patients. The first sets of ECIL slides about the management of invasive fungal disease were made available on the web in 2006 and the papers were published in 2007. The third meeting of the group (ECIL 3) was held in September 2009 and the group updated its previous recommendations. The goal of this paper is to summarize the new proposals from ECIL 3, based on the results of studies published after the ECIL 2 meeting: (1) the prophylactic recommendations for hematopoietic stem cell transplant recipients were formulated differently, by splitting the neutropenic and the GVHD phases and taking into account recent data on voriconazole; (2) micafungin was introduced as an alternative drug for empirical antifungal therapy; (3) although several studies were published on preemptive antifungal approaches in neutropenic patients, the group decided not to propose any recommendation, as the only randomized study comparing an empirical versus a preemptive approach showed a significant excess of fungal disease in the preemptive group.
*Bone Marrow Transplantation* (2011) 46, 709-718; doi:10.1038/bmt.2010.175; published online 26 July 2010
**Keywords:** antifungals; neutropenia; leukemia; SCT; *Candida*; *Aspergillus*

## Introduction

Hematology patients and hematopoietic stem cell transplant (HSCT) recipients represent a population at high risk for invasive fungal disease (IFD). Given the high morbidity and mortality of *Candida* and *Aspergillus* infections, the availability of new antifungals and the rich scientific production on this topic, there is a need for a regular update of consensus guidelines.

In 2005, several groups, including the European Group for Blood and Marrow Transplantation, the European Organization for Treatment and Research of Cancer, the European Leukemia Net and the Immunocompromised Host Society created the European Conference on Infections in Leukemia (ECIL). These groups are all involved in the management and research programs in leukemia and

# ANTİFUNGAL KULLANIM PROFİLİ

- Pediatrik grup, 2007-2009, hematolojik malinite
- AFT- %31; %75 Ampirik
- %30'unda KURTARMA
- %45 PFX- %72 FLC

*Cesario S, Pagano L, et al. Clin Infect Dis 2009;48:1042-51.*

# Sonuçlar

- 11/293 ölüm - 3'ü IFI ilişkili, 3'üde pre-emptif kolda
- Toplam; %5.8 IFI-17 olgu, 12'si IA (%70'inde radyolojik bulgu, 5'i ind. tedavi alanlarda)
- Güvenilirlik ; %34.5 ≤60mL/sa.

*Cordonnier C, et al. Clin Infect Dis 2009;48:1042-51.*

- **Kontrolsüz, prospektif, çok merkezli**
- **190 ve 207 hasta, hematolojik malinite**
- **İki tedavi stratejisinin klinik kullanım ve etkinliği (IFI sıkılığı ve mortalite)**
- **Ampirik; persistan ateş**
- **Pre-emptif; laboratuvar veya radyolojik veri**
- **Mortalite; 12. hafta**

***Pagano L, et al. Haematologica 2011;96(9):1366-70.***

# Sonuçlar

- Hematolojik malignitelerde - Ampirik tedavi >Pre-emptif
- Pre-emptif tedavi nedeni; %78 CT, %16 GM
- İndüksiyon KT alanlarda IFI insidansı daha yüksek, sağkalım daha düşük
- Toksisite verisi yok

*Pagano L, et al. Haematologica 2011;96(9):1366-70.*

tissue

Host factors + Clinical features + Mycology = Proven

Host factors + Clinical features + Mycology = Probable

Host factors + Clinical features  = Possible

Host factors + Clinical features =

Host factors + Mycology =

Host factors =

Not classified

# Mikoloji

Doku aspiratı ,BAL, balgam KÜLTÜR

Kan,, BAL. BOS antijen

sinus aspiratında küf

Mikoloji

BAL. BOS veya kan :Beta-D-glucan in

Doku veya or sterile sıvı örneklerinde küf

PCR : valide olana kadar kriter değil

# Tanısal Testler: KULLANMA AMACI?

## TARAMA TESTİ?

- ERKEN TANI

## TANI TESTİ?

- DOĞRULAYACAK BİR DİĞER TEST

# Tanısal Testler: Sorunlar Belirsizlikler

- Orta derecede duyarlı (%50)
- Altta yatan hastalık
- Profilaktik tedavi
- GM: PPD: Prevalans %5 → %31
  Prevalans %20 → %69
- Tarama testlerinin kullanılabilmesi için prevalans %5-10 olmalı
- ALLO KHN, AML, rölaps ve agresif KT alacak hastalar

*Pfeiffer CD. CID 2006*

# Yüksek Riskli Hasta Monitorizasyonunda Galaktomannan

| Parameter | Description |
|---|---|
| Population | Prolonged neutropenia, allogeneic SCT |
| Frequency | Two or three times weekly during high level immunosuppression |
| Criteria for positivity | Two consecutive serum specimens with GMI≥0.5 |
| | Always repeat the test before implementing therapy for invasive aspergillosis |
| Considerations | The galactomannan antigenemia EIA does not replace other tests in the workup of invasive aspergillosis |
| | Antibiotics produced by *Penicillium* spp. may cause false-positivity |
| | Medications/IV additives containing materials produced by *Aspergillus* (sodium gluconate) or *Penicillium* (certain antibiotics) may cause false-positivity |
| | Histoplasmosis (and other endemic mycoses) may cause false-positivity |
| | Mold-active antifungal drugs may cause false-negativity: repeat the test before implementing therapy for invasive aspergillosis |
| | Falsely-positivity or falsely-negativity may occur for other reasons: clinical correlation is imperative |



***Eur J Clin Microbiol Infect Dis 2008;27:245-251***

JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2009, p. 129–133 Vol. 47, No. 1
0095-1137/09/$08.00+0 doi:10.1128/JCM.00506-08


# Utility of Galactomannan Enzyme Immunoassay and (1,3) β-D-Glucan in Diagnosis of Invasive Fungal Infections: Low Sensitivity for *Aspergillus fumigatus* Infection in Hematologic Malignancy Patients▽

R. Y. Hachem,* D. P. Kontoyiannis, R. F. Chemaly, Y. Jiang, R. Reitzel, and I. Raad

TABLE 3. Performances of GM enzyme immunoassay and BG test for patients infected with different organisms (per sample)

| Test and organism | Sensitivity (%) | Specificity (%) | PPV (%)[a] | NPV (%)[a] |
|---|---|---|---|---|
| GM enzyme immunoassay | | | | |
| *A. fumigatus* ($n = 69$) | 13 | 99 | 90 | 66 |
| Non-*fumigatus Aspergillus* species ($n = 39$) | 49 | 99 | 95 | 86 |
| Other mold ($n = 77$) | 6 | 99 | 83 | 62 |
| BG test | | | | |
| *A. fumigatus* ($n = 69$) | 61 | 88 | 75 | 79 |
| Non-*fumigatus Aspergillus* species ($n = 39$) | 64 | 88 | 64 | 88 |
| Other mold ($n = 76$) | 47 | 88 | 72 | 72 |

[a] PPV, positive predictive value; NPV, negative predictive value.

# SORU: Tek bir GM (+) olan hastada IA riski?

- Spesifite %95
- Sensitivite %80
- Prevalans %5

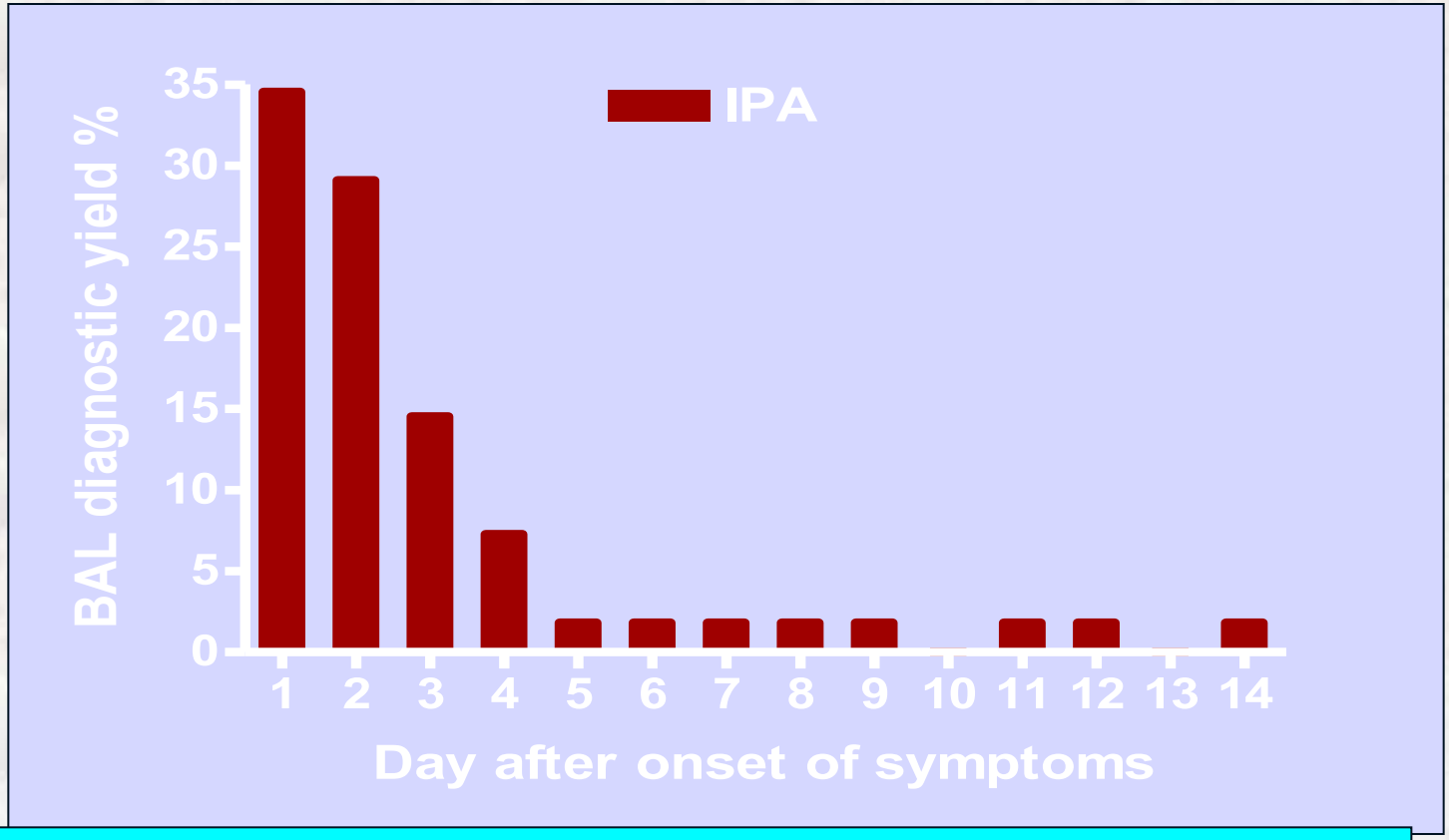
**CEVAP: %20**

# SORU: Tek bir GM (-) olan hastada IA olmama olasılığı?

- Spesifite %95
- Sensitivite %80
- Prevalans %5

**CEVAP: %95**

# BAL Zamanlaması ve IPA Tanısı




Shannon V & Kontoyiannis DP, unpublished

# Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

**Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lortholary, Christina Rieger, Angelika Boehme, Mickael Aoun, Heinz-August Horst, Anne Thiebaut, Markus Ruhnke, Dietmar Reichert, Nicola Vianelli, Stefan W. Krause, Eduardo Olavarria, and Raoul Herbrecht, for the AmBiLoad Trial Study Group***

**(See the editorial commentary by Anaissie on pages XXX–XX)**

***Background.*** Treatment of invasive mold infection in immunocompromised patients remains challenging. Voriconazole has been shown to have efficacy and survival benefits over amphotericin B deoxycholate, but its utility is limited by drug interactions. Liposomal amphotericin B achieves maximum plasma levels at a dosage of 10 mg/kg per day, but clinical efficacy data for higher doses are lacking.

***Methods.*** In a double-blind trial, patients with proven or probable invasive mold infection were randomized to receive liposomal amphotericin B at either 3 or 10 mg/kg per day for 14 days, followed by 3 mg/kg per day. The primary end point was favorable (i.e., complete or partial) response at the end of study drug treatment. Survival and safety outcomes were also evaluated.

***Results.*** Of 201 patients with confirmed invasive mold infection, 107 received the 3-mg/kg daily dose, and 94 received the 10-mg/kg daily dose. Invasive aspergillosis accounted for 97% of cases. Hematological malignancies were present in 93% of patients, and 73% of patients were neutropenic at baseline. A favorable response was achieved in 50% and 46% of patients in the 3- and 10-mg/kg groups, respectively (difference, 4%; 95% confidence interval, −10% to 18%; $P > .05$); the respective survival rates at 12 weeks were 72% and 59% (difference, 13%; 95% confidence interval, −0.2% to 26%; $P > .05$). Significantly higher rates of nephrotoxicity and hypokalemia were seen in the high-dose group.

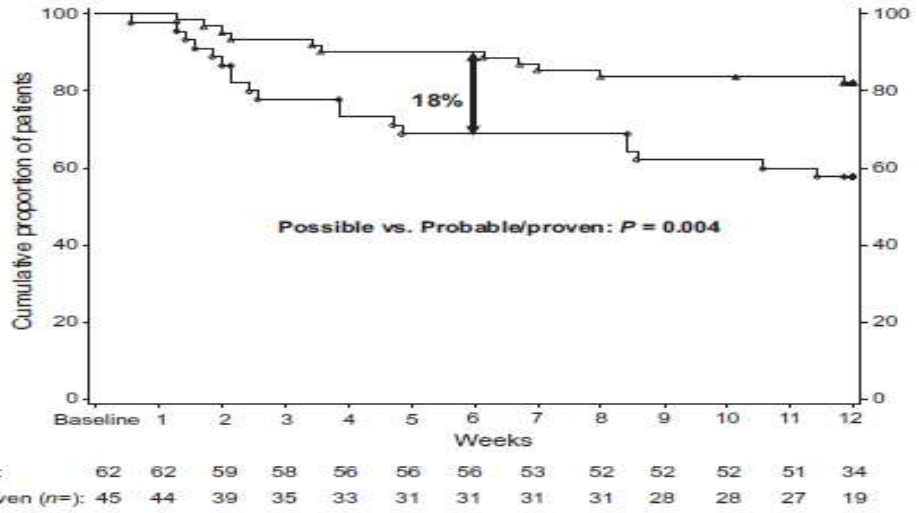
***Conclusions.*** In highly immunocompromised patients, the effectiveness of 3 mg/kg of liposomal amphotericin B per day as first-line therapy for invasive aspergillosis is demonstrated, with a response rate of 50% and a 12-week survival rate of 72%. The regimen of 10 mg/kg per day demonstrated no additional benefit and higher rates of nephrotoxicity.

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases
Original article

# Efficacy outcomes in a randomised trial of liposomal amphotericin B based on revised EORTC/MSG 2008 definitions of invasive mould disease

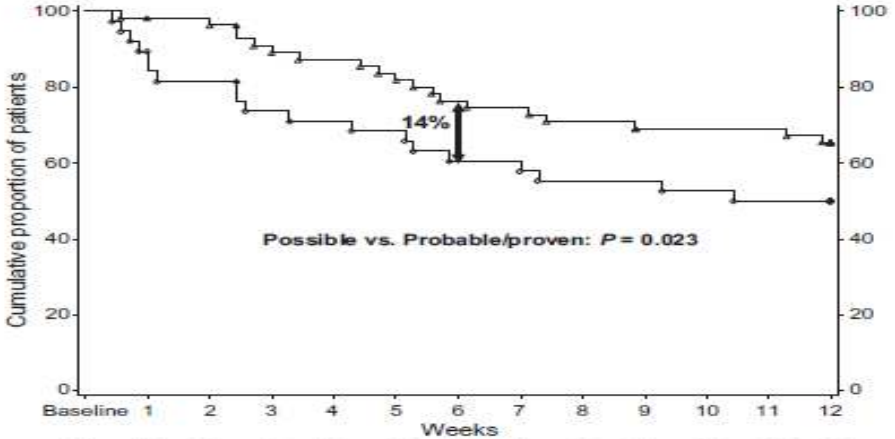
Oliver A. Cornely,[1,2,3] Johan Maertens,[4] Mark Bresnik,[5] Ramin Ebrahimi,[5] Emma Dellow,[6] Raoul Herbrecht[7] and J. Peter Donnelly[8]

The results of this study show that cases of possible IFD respond better to liposomal amphotericin B than do cases of probable/proven IFD irrespective of the dose initially given. This is likely to be due to treating the infection at an early stage. Moreover, survival at 6 and 12 weeks was also better.




△ Possible (*n*=): 62 62 59 58 56 56 56 53 52 52 52 51 34
◇ Probable/Proven (*n*=): 45 44 39 35 33 31 31 31 31 28 28 27 19

**Figure 1** Probability of survival in patients treated with liposomal amphotericin B 3 mg kg$^{-1}$ QD.




△ Possible (*n*=): 56 54 53 49 48 45 42 41 39 37 37 37 24
◇ Probable/Proven (*n*=): 38 32 31 28 27 26 23 22 21 21 20 19 14

**Figure 2** Probability of survival in patients treated with liposomal amphotericin B 10 mg kg$^{-1}$ QD.

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Bone Marrow Transplantation (2011) 46, 709–718

www.nature.com/bmt

ORIGINAL ARTICLE

BII

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### Introduction

Hematology patients and hematopoietic stem cell transplant (HSCT) recipients represent a population at high risk for invasive fungal disease (IFD). Given the high morbidity and mortality of *Candida* and *Aspergillus* infections, the availability of new antifungals and the rich scientific production on this topic, there is a need for a regular update of consensus guidelines.

In 2005, several groups, including the European Group for Blood and Marrow Transplantation, the European Organization for Treatment and Research of Cancer, the European Leukemia Net and the Immunocompromised Host Society created the European Conference on Infections in Leukemia (ECIL). These groups are all involved in the management and research programs in leukemia and




# EMPİRİK ANTİFUNGAL TEDAVİ

VORİKONAZOL

LİPO-AMFO

# PRE-EMPTİF ANTİFUNGAL TEDAVİ

# EAFT: ECIL-4

| Antifungal agent | Daily dose | Level of recommendation | CDC grading level of evidence for Efficacy | Safety |
|---|---|---|---|---|
| Ampho B deoxy | 0.5-1 mg/kg iv | B/D | I | I |
| Liposomal AmB | 3 mg/kg iv | A | I | I |
| ABLC | 5 mg/kg iv | B | I | I |
| ABCD | 4 mg/kg iv | B | I | I |
| Fluconazole | 400 mg iv | C | I | I |
| Itraconazole | 200 mg iv | B | I | I |
| Voriconazole | 2 x 3 mg/kg iv | B | I | I |
| Caspofungin | 50 mg | A | I | I |
| Micafungin | 100 mg | B | II | II |

*Maertens J et al. Bone Marrow Transpl. 2011*

Table 3. Empirical therapy for patients with suspected IFDs.

| Drugs | IDSA (Walsh et al., 2008) | IDSA (Pappas et al., 2009) | BCSH (Prentice et al., 2008) | ECIL-3 (Maertens et al., 2010) |
|---|---|---|---|---|
| Fluconazole | | ✓B[b] (P516, IV recommendation 19) | | ✓C (P713, Table 3) |
| Itraconazole | ✓A[a] (P347, RH column) | ✓B[b] (P516, IV recommendation 19) | | ✓B (P713, Table 3) |
| Voriconazole | ✓A[a] (P347, RH column) | | | ✓B (P713, Table 3) |
| Amphotericin B | ✓A[a] (P347, RH column) | | | ✓B[c] (P713, Table 3) |
| Amphotericin B colloidal dispersion | ✓A[a] (P347, RH column) | | | ✓B (P713, Table 3) |
| Amphotericin B lipid complex | ✓A[a] (P347, RH column) | ✓A[b] (P516, IV recommendation 18) | | ✓B (P713, Table 3) |
| Liposomal amphotericin B | ✓A[a] (P347, RH column) | ✓A[b] (P516, IV recommendation 18) | ✓A[d] (P36) | ✓A (P713, Table 3) |
| Caspofungin | ✓A[a] (P347, RH column) | ✓A[b] (P516, IV recommendation 18) | ✓A[cd] (P36) | ✓A (P713, Table 3) |
| Micafungin | | | | ✓B (P713, Table 3) |

Empirical therapy was defined as persistent neutropenic fever despite broad-spectrum antibiotics

# ASPERGİLLOZ; AMPİRİK TEDAVİ (NÖTROPENİ + ATEŞ + >96 SAAT AB YANITSIZ)

| | ECIL | ESCMID |
|---|---|---|
| L-AmfoB | AI | BI |
| Caspofungin | AI | AI |
| ABLC | BI | CI |
| ABCD | BI | CI |
| AmfoB-d | BI/DI* | DI |
| Itrakonazol | BI | CII |
| Vorikonazol | BI | BII |
| Mikafungin | BII | BII |

# EAFT-UZLAŞI VE SORUNLAR

Table 3. (Continued).

| Topic discussed | Consensus | Conflict/unresolved issues |
|---|---|---|
| Impact of empirical therapy on patient outcome | Lack of good quality evidence to support impact of empirical antifungal treatment on patient outcome (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010; Prentice et al., 2008; Slavin et al., 2008; Böhme et al., 2009; Cornely et al., 2009) | This lack of evidence has been interpreted in different ways. BSCH discourages empirical therapy, and IDSA recommend it only for high risk patients despite the lack of good quality evidence (Prentice et al., 2008; Walsh et al., 2008; Pappas et al., 2009) |
| Time to initiation of empirical therapy | Persistent fever of unknown origin unresponsive to broad-spectrum antibiotics (Prentice et al., 2008; Slavin et al., 2008; Böhme et al., 2009; Cornely et al., 2009; Maertens et al., 2010) | No specification in IDSA: no recommendation in BCSH (Walsh et al., 2008; Pappas et al., 2009; Prentice et al., 2008) |
| Criteria for choosing empirical therapy | Efficacy and safety are the main considerations (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010) | Additional factors considered are: activity against *Candida* and *Aspergillus* (the two most common fungal pathogens in this group of patients) by IDSA and ECIL-3; and cost by ECIL-3 (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010) |
| Choice of empirical agent | Caspofungin and liposomal amphotericin B are common choices with good evidence (A) (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010) | Although voriconazole failed to achieve non-inferiority when compared with liposomal amphotericin B, it is still included in ECIL and IDSA because it is the drug of choice for invasive aspergillosis and it reduces the incidence of breakthrough IFD. ECIL-3 and IDSA also recommend fluconazole for its activity against *Candida*; and itraconazole for its similar efficacy, though acknowledging problems with absorption and toxicity (Walsh et al., 2008; Pappas et al., 2009; Maertens et al., 2010) |

# TÜRKİYE-UZMAN GÖRÜŞÜ

Türkiye (UZMAN GÖRÜŞLERİ):

"Tanı güdümlü (preemptif) yaklaşım için farklı ünitelerde tanı araçlarına ulaşmada zorluklar söz konusu olduğundan, yüksek riskli hastalarda ampirik tedavi başlanıp, tanı testlerinden elde edilecek sonuçlara göre gerekli uyarlamaların yapılması daha doğru olur"

***Turk J Hematol***

***2014;31:111-120***

# Evidence-based approach to treatment of febrile neutropenia in hematologic malignancies

*Juan Gea-Banacloche*[1]

Practicing evidenced-based medicine means "integrating individual clinical expertise with the best available external clinical evidence from systematic research."[1] This definition acknowledges that anyone's

2013

[1]*Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Applying the principles of evidence-based medicine to febrile neutropenia (FN) results in a more limited set of practices than expected. Hundreds of studies over the last 4 decades have produced evidence to support the following: (1) risk stratification allows the identification of a subset of patients who may be safely managed as outpatients given the right health care environment; (2) antibacterial prophylaxis for high-risk patients who remain neutropenic for ≥ 7 days prevents infections and decreases mortality; (3) the empirical management of febrile neutropenia with a single antipseudomonal beta-lactam results in the same outcome and less toxicity than combination therapy using aminoglycosides; (4) vancomycin should not be used routinely empirically either as part of the initial regimen or for persistent fever, but rather should be added when a pathogen that requires its use is isolated; (5) empirical antifungal therapy should be added after 4 days of persistent fever in patients at high risk for invasive fungal infection (IFI); the details of the characterization as high risk and the choice of agent remain debatable; and (6) preemptive antifungal therapy in which the initiation of antifungals is postponed and triggered by the presence, in addition to fever, of other clinical findings, computed tomography (CT) results, and serological tests for fungal infection is an acceptable strategy in a subset of patients. Many practical management questions remain unaddressed.

## Table 4. Evidence-based recommendations for FN syndromes

| Fever and neutropenia syndrome | Treatment recommendation from guidelines | Grading according to guidelines | | | | |
|---|---|---|---|---|---|---|
| | | ESMO[14] | IDSA[13] | Australian[44] | NCCN[45]* | IPNP[20]† |
| First fever in patients at high risk of complications | Monotherapy with intravenous anti-*Pseudomonas* beta-lactam | I, A | A-I | A | 1 2B for ceftazidime | 1A |
| | Avoid routine use of vancomycin | NA | A-I | A | 2A | 1A |
| | In special circumstances diverse combinations are recommended | NA | B-III or C-III | D | 2A | 1B |
| Persistent fever in patients at high risk for invasive fungal infections | Add empirical antifungal coverage | II, A | A-I | NA | 2A | 1C† |
| | Preemptive approach (withhold antifungals if no investigations negative) | NA | B-II | NA | NA | NA† |
| Recurrent fever | Not addressed by the guidelines separately from persistent fever | | | | | |
| | Expert opinion recommends changing the antibacterial and antifungal regimen and looking for superinfection, including viral | | | | | |
| Engraftment fever | Not addressed by the guidelines | | | | | |
| | Expert opinion recommends: look for preexistent focus, rule out superinfection, consider engraftment syndrome | | | | | |

The ASCO Guidelines[17] are not included because they refer specifically to outpatient management and do not offer grading of the recommendations. The Australian guidelines do not specify grading of recommendation for the empirical addition of antifungal agents during FN, but they have published detailed pathogen-specific antifungal management advice.[26]

IPN indicates International Pediatric Fever and Neutropenia Guideline Panel for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem Cell Transplantation; and NA, not addressed. For definitions of the fever and neutropenia syndromes, see text.

*The NCCN guidelines address only prophylaxis; the recommendations in this table are from the online version accessed May 3, 2013 at www.nccn.org.

†The pediatric panel different grading of these recommendations reflects the lack of pediatric-specific data.

Table 3. Examples of clinical scenarios in FN for which evidence-based recommendations are not available

| | | |
|---|---|---|
| 1 | A 62-year-old man with hairy cell leukemia and prolonged neutropenia was admitted for evaluation. Only prophylaxis was oral fluconazole. The day after admission, he developed his first fever. Blood cultures obtained and ceftazidime started. The blood cultures grew susceptible *E coli*. | Should this patient antibiotic treatment be "downgraded" to ceftriaxone or ciprofloxacin? |
| 2 | A patient with AML in first remission was admitted for allogeneic stem cell transplantation and started on prophylactic levofloxacin. Known carrier of VRE. First fever on day +6. Hemodynamically stable and asymptomatic. | Should VRE coverage be included as part of the initial antibiotic regimen? |
| 3 | A patient with relapsed AML and a history of invasive aspergillosis was admitted for reinduction. ANC $< 100$. Prophylaxis with levofloxacin and caspofungin. A CT-PET showed a new pulmonary nodule. Afebrile. | What is the best diagnostic and therapeutic strategy for this patient? |
| 4 | 18-year-old man with refractory ALL was transferred for a phase 1 clinical trial. He had been on cefepime and metronidazole for typhlitis in another hospital. Fluconazole prophylaxis. Forty-eight hours after admission, he developed a new fever and worsening abdominal pain. | What change (if any) should be made to his antibacterial coverage? What change (if any) should be made to his antifungal coverage? |
| 5 | A 28-year-old woman with AML had been in the hospital for several weeks undergoing myeloablative stem cell transplantation. She experienced VRE bacteremia and urinary tract infection with an ESBL-producing *Klebsiella pneumoniae*. She was on meropenem, daptomycin, and caspofungin. Afebrile for the last week, she seemed to be engrafting. She developed a new fever and the CT showed new patchy multifocal pulmonary infiltrates. | Should another antifungal be substituted or added? Should the antibacterial coverage be modified? |

All patients were seen by the author at the NIH Clinical Center. Patient 1 was downgraded to ceftriaxone; patient 2 was treated with piperacillin-tazobactam and defervesced uneventfully; patient 3 was started on voriconazole, but the bronchoalveolar lavage showed *Cunninghamella* and he was successfully treated for mucormycosis with liposomal amphotericin B and surgical resection; patient 4 had *Enterococcus faecalis* bacteremia; patient 5 had CMV pneumonitis.

AML indicates acute myelogenous leukemia; VRE, vancomycin-resistant enterococcus; ANC, absolute neutrophil count; and ALL, acute lymphocytic leukemia.

Bone Marrow Transplantation (2011) 46, 709–718

www.nature.com/bmt

ORIGINAL ARTICLE

# European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 Update

J Maertens[1], O Marchetti[2], R Herbrecht[3], OA Cornely[4], U Flückiger[5], P Frêre[6], B Gachot[7], WJ Heinz[8], C Lass-Flörl[9], P Ribaud[10], A Thiebaut[11] and C Cordonnier[12], on behalf of the third European

**Table 3** ECIL 3 guidelines on empirical antifungal treatment in neutropenic patients with persistent or relapsing fever (the updated items are reported in bold italic)

| *Antifungal agent* | *Daily dose* | *Level of recommendation* | *CDC grading Level of evidence for* | |
|---|---|---|---|---|
| | | | *Efficacy* | *Safety* |
| Liposomal ampho B | 3 mg/kg | A[a] | I | I |
| Caspofungin | 50 mg | A[a,b] | I | I |
| ABCD | 4 mg/kg | B[c] | I | I |
| ABLC | 5 mg/kg | B[c] | I | I |
| Itraconazole | 200 mg i.v. | B[b,c] | I | I |
| Voriconazole | 2 × 3 mg/kg i.v. | B[b,d,e] | I | I |
| ***Micafungin*** | ***100 mg*** | ***B*** | ***II*** | ***II*** |
| Ampho B deoxycholate | 0.5–1 mg/kg | B[c]/D[f] | I | I |
| Fluconazole | 400 mg i.v. | C[b,c,g] | I | I |

# Guidelines on the management of invasive fungal infection during therapy for haematological malignancy

British Committee for Standards in Haematology

**Date for guideline review**

March 2010

If empirical antifungal therapy is given it is desirable to minimise the toxicity of this therapy since the majority of patients never have IFI confirmed. Therefore the choice of empirical therapy is between liposomal amphotericin B (but not in escalated initial doses) and caspofungin, the latter having the superior (ie lower) toxicity profile (grade A, level Ib)

## Primary objective

To estimate the rate of occurrence of possible, probable and proven IMD among patients expected to develop ≥7 days neutropenia after receiving chemotherapy to induce or maintain remission of AML or MDS or conditioning therapy to prepare for an allogeneic HSCT.

**PIMDA Results:**
**1243 pts: 6.6% probable/proven**

**Still mostly treating possible cases...**

Donnelly et al. 2014 ECCMID Poster# P0028a


ANTİFUNGAL AJANLAR
İMMÜN İYİLEŞMEYE KADAR
BİR KÖPRÜ GİBİ

J Antimicrob Chemother 2011; **66** Suppl 1: i55–58
doi:10.1093/jac/dkq442

Journal of Antimicrobial Chemotherapy

# Managing invasive fungal infections: relying on clinical instincts or on a rational navigation system?

**Ben E. de Pauw[1]* and Claudio Viscoli[2]**

[1]*Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;* [2]*Infectious Diseases Division, San Martino University Hospital, University of Genoa, Genova, Italy*

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The management of invasive fungal disease in the immunocompromised host is complex and requires the specialized knowledge of physicians whose primary interest is actually the underlying disease rather than infectious complications. This Supplement aims to provide these physicians with some tools that may help to guide them through the maze of suspicion that an invasive fungal disease is present by offering an integrated care pathway of rational patient management. Such pathways will inevitably vary in detail in different centres and depend for their success on the presence of multidisciplinary teams and an explicit agreement on at least the minimum requirements for effective management. The integrated care pathways presented constitute an objective instrument to allow regular audits for recognizing opportunities to change practice if and when weaknesses are identified.

**Keywords:** invasive fungus, guidelines, antifungal therapy, immunodeficiency

J Antimicrob Chemother 2011; 66 Suppl 1: i45–53
doi:10.1093/jac/dkq441

Journal of Antimicrobial Chemotherapy

# INTEGRATED CARE PATHWAY

Samir Agrawal[1]*, William Hope[2], János Sinkó[3] and Christopher Kibbler[4]

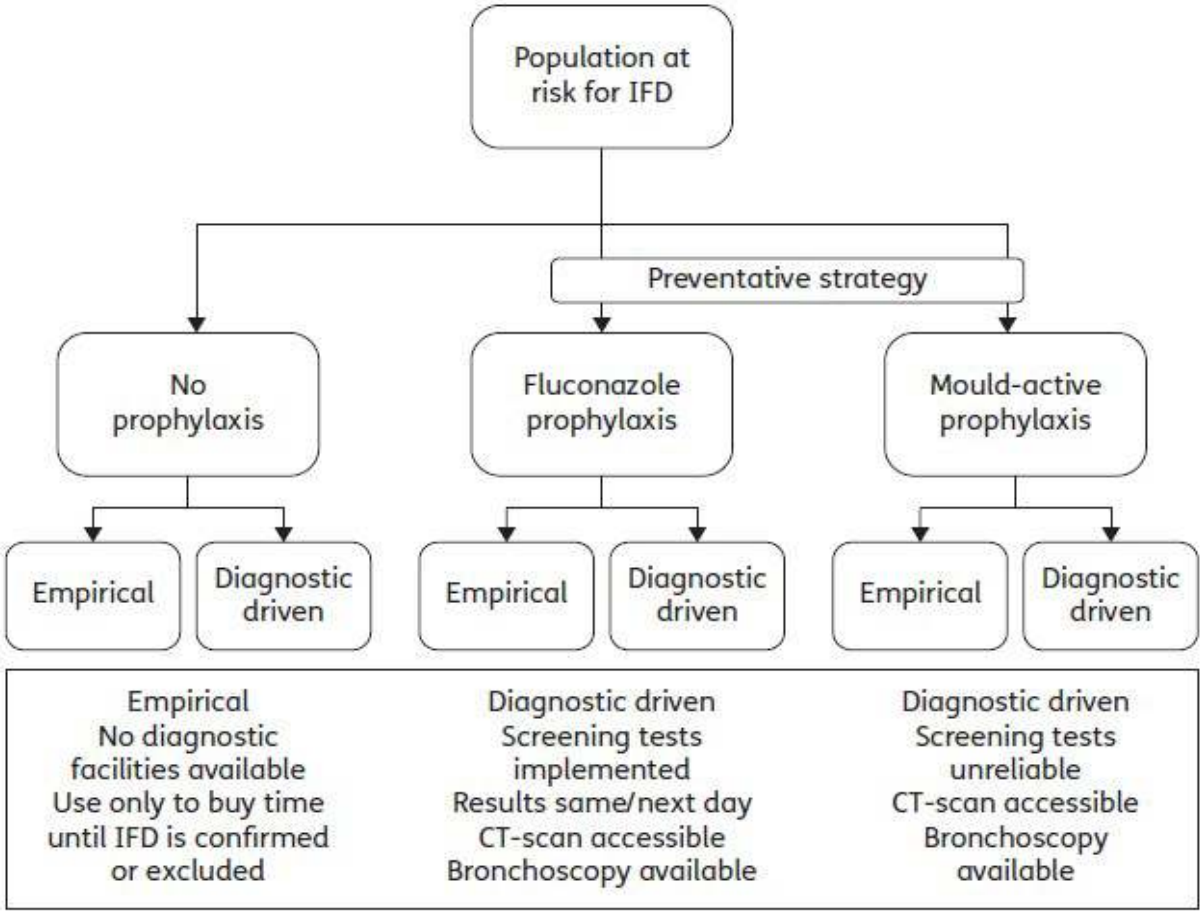



**Figure 1.** Antifungal strategies for patients at risk of invasive fungal disease (IFD).

J Antimicrob Chemother 2011; 66 Suppl 1: i45–53
doi:10.1093/jac/dkq441

Journal of Antimicrobial Chemotherapy

# INTEGRATED CARE PATHWAY

Samir Agrawal[1]*, William Hope[2], János Sinkó[3] and Christopher Kibbler[4]

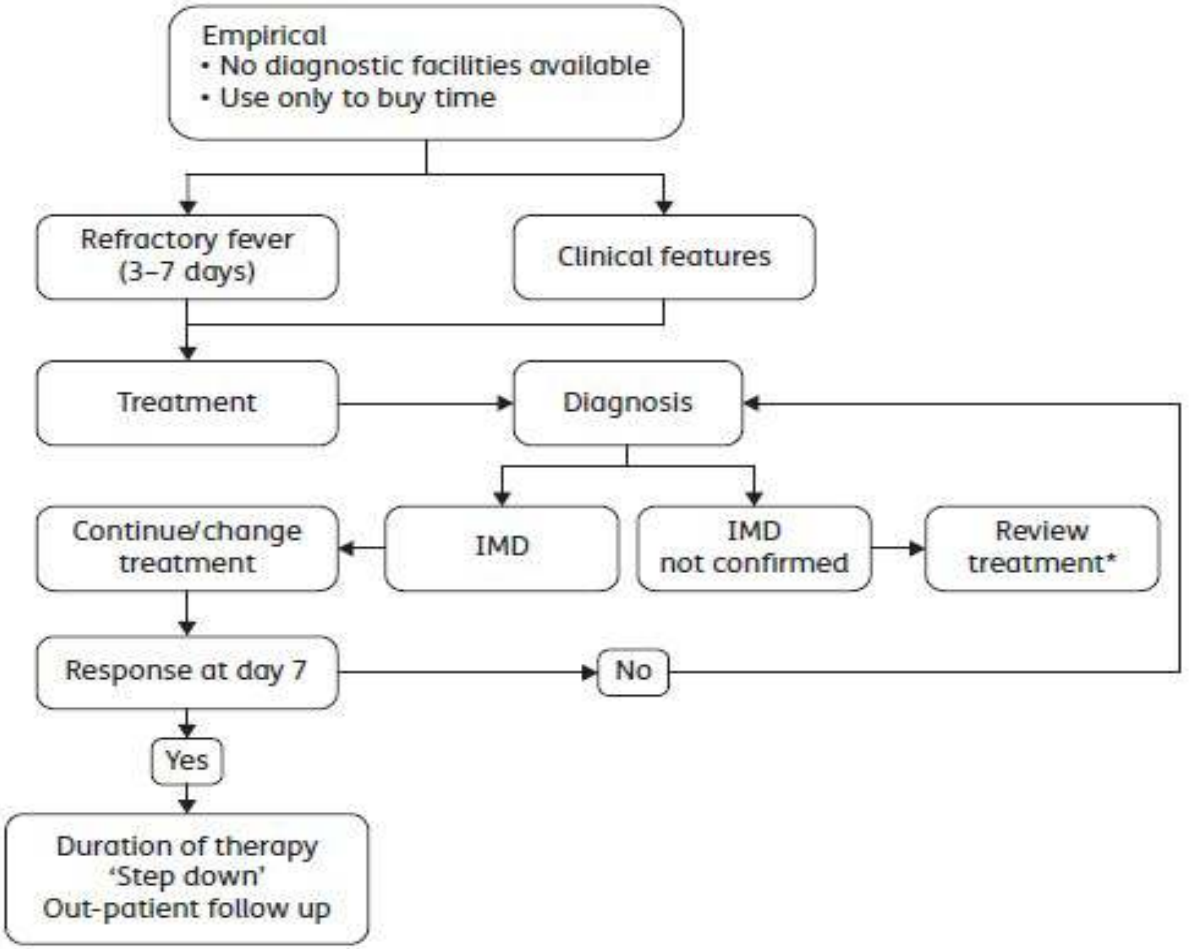



**Figure 2.** Empirical antifungal therapy integrated care pathway. *Multidisciplinary team input important at this stage.

J Antimicrob Chemother 2011; 66 Suppl 1: i45–53
doi:10.1093/jac/dkq441

Journal of Antimicrobial Chemotherapy

# INTEGRATED CARE PATHWAY

Samir Agrawal[1]*, William Hope[2], János Sinkó[3] and Christopher Kibbler[4]

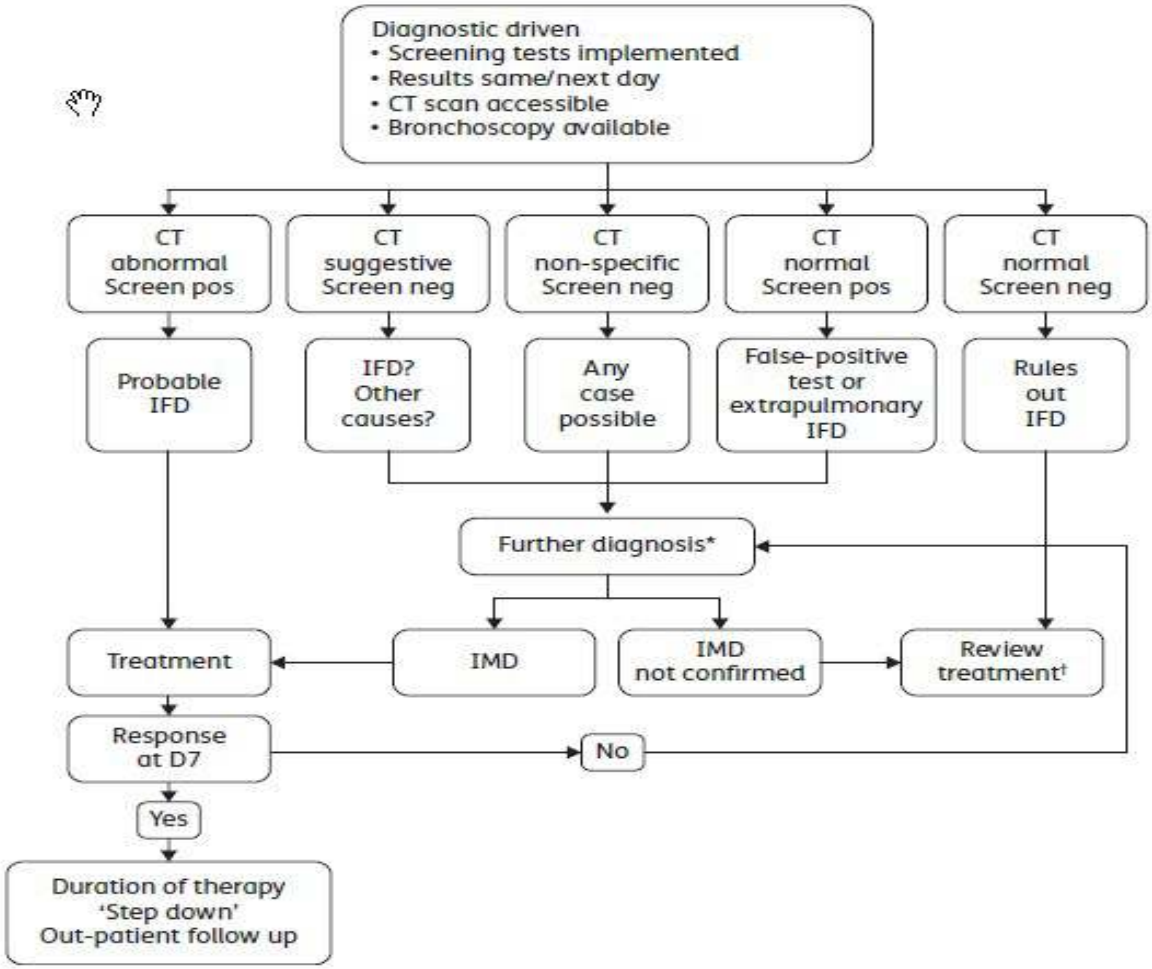



**Figure 3.** Diagnostic-driven antifungal therapy integrated care pathway. IFD, invasive fungal disease. *Further diagnosis could include bronchoscopy with bronchoalveloar lavage, calcofluor testing, galactomannan antigen, PCR and image-guided or surgical biopsy of any lesions. †Multidisciplinary team input important at this stage.

# Current International Guidelines

| | ECIL 2009 | IDSA 2010 | NCCN 2013 |
|---|---|---|---|
| Empirical | B II | A I (for high risk) | Recommended |
| Pre-emptive | No Grading | B II (in a subset of high risk pts only) | Not recommended |

# Ampirik vs Preemptif (Tanı güdümlü) AF Tedavi

## IDSA FEN rehberi:

Beklenen nötropeni süresi >7 gün, 4-7 gündür ABtdv'ne rağmen ateşi düşmeyen hastalara antifungal verilmeli (AI)

Hastanın durumu stabil, görüntüleme veya serolojik olarak mantar inf bulgusu yoksa, kültürde mantar üretilmedi ise antifungal ajan bekletilebilir (BII)

## Türkiye (uzman görüşleri):

"Tanı güdümlü (preemptif) yaklaşım için farklı ünitelerde tanı araçlarına ulaşmada zorluklar söz konusu olduğundan, yüksek riskli hastalarda ampirik tedavi başlanıp, tanı testlerinden elde edilecek sonuçlara göre gerekli uyarlamaların yapılması daha doğru olur"

Turk J Hematol 2014;31:111-120

# Empirik tedavide ilaç tercihi yapılırken dikkate alınması gerekenler:

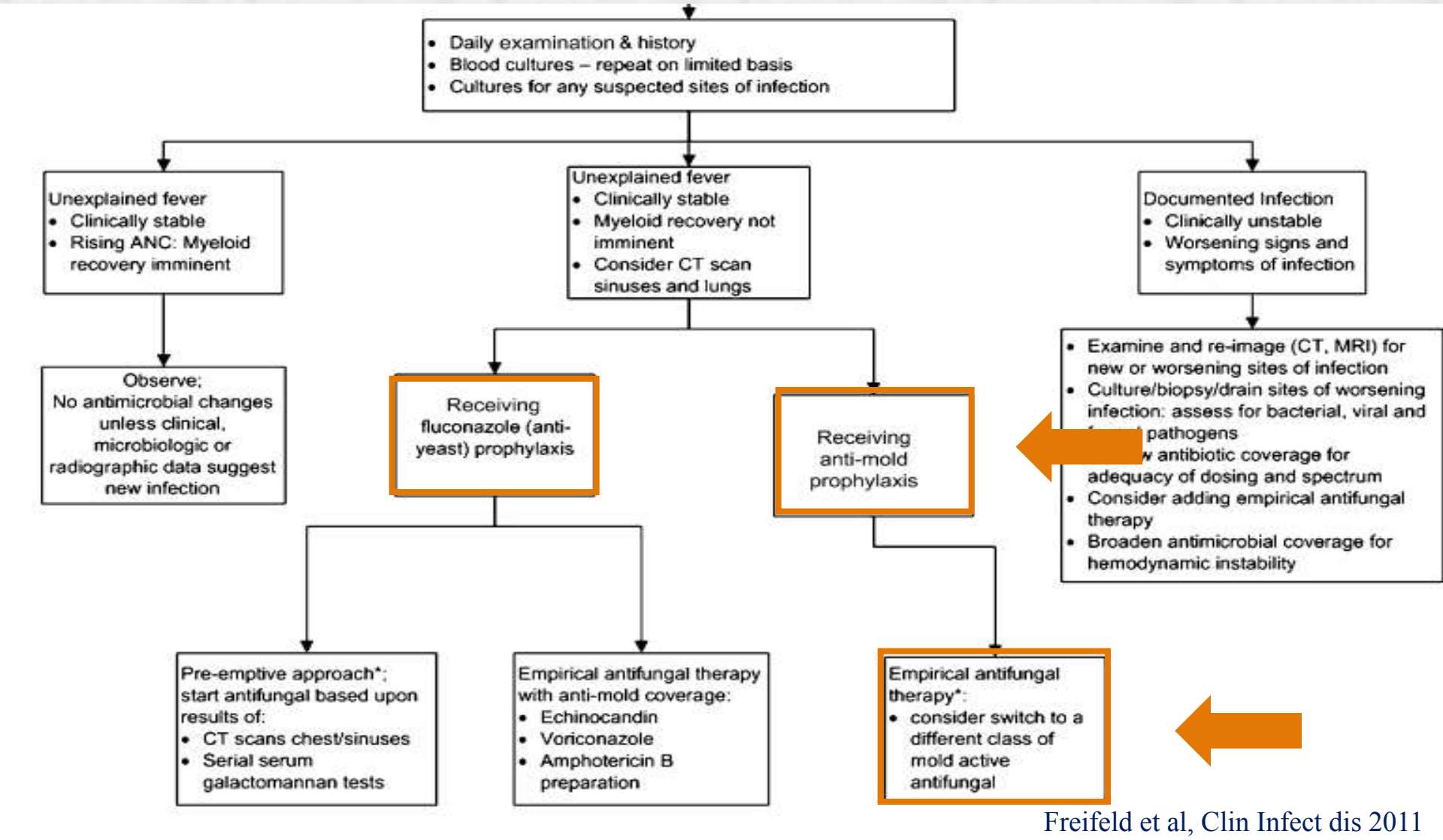
**Table 3** | Factors to be considered when selecting an antifungal agent for empirical treatment

| Epidemiology of invasive fungal infection (IFI) | *Candida*<br>*Aspergillus*<br>Other filamentous fungi | | |
|---|---|---|---|
| **Spectrum of the antifungal** | ***Candida*** | ***Aspergillus*** | **Other filamentous fungi** |
| Amphotericin B | +++ | +++ | +++ |
| Voriconazole | +++ | +++ | ++ |
| Caspofungin | +++ | +++ | - |
| **Type of activity** | **Yeasts** | | **Filamentous fungi** |
| Amphotericin B | Fungicidal | | Fungicidal |
| Voriconazole | Fungistatic | | Fungicidal |
| Caspofungin | Fungicidal | | Fungistatic |
| **Clinical experience** | **Efficacy against *Aspergillus*** | | **Breakthrough aspergillosis and mucormycosis** |
| Amphotericin B | + + + | | - |
| Voriconazole | + + + | | + |
| Caspofungin | + + | | + |
| **Severity of infection** | For empirical treatment select the antifungal agent with the highest efficacy and the broadest spectrum of action | | |
| **Prophylaxis with triazole or candin** | In case of suspected IFI begin with liposomal amphotericin B | | |

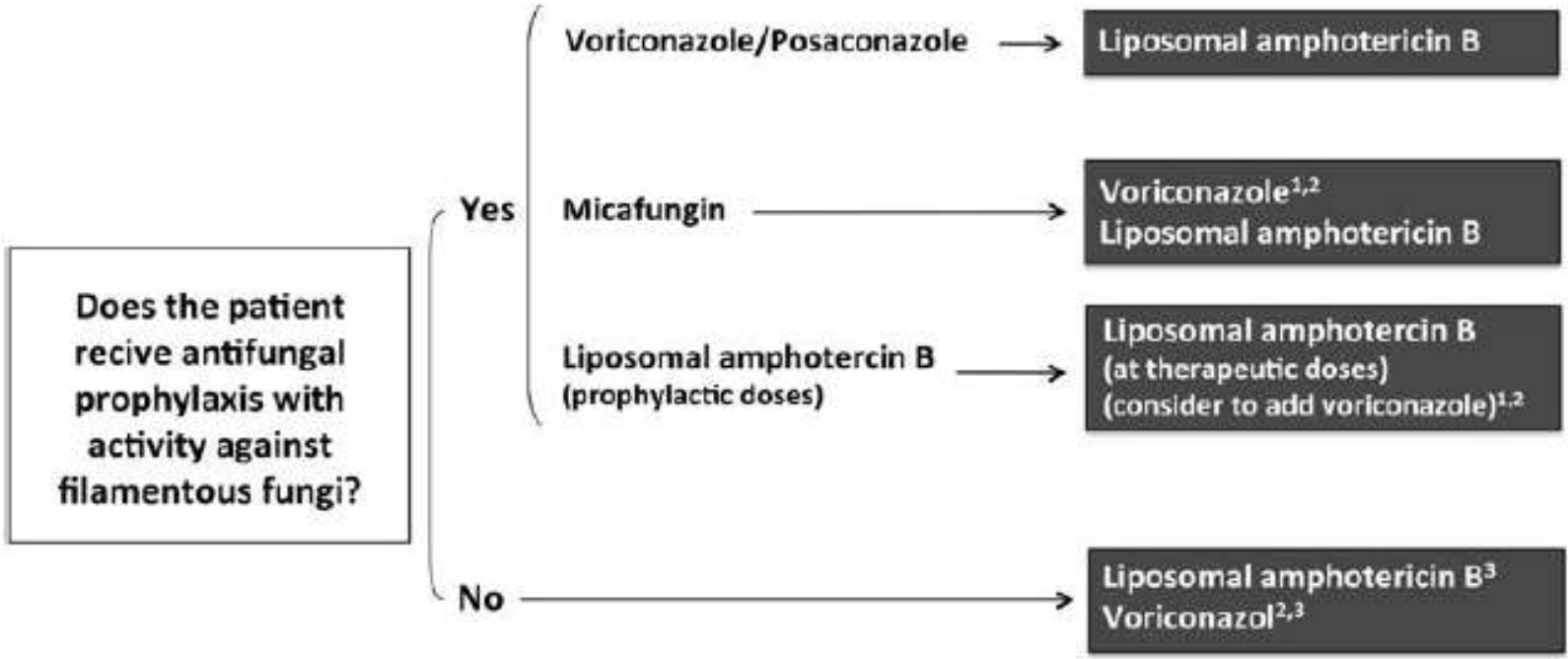
# Posakonazol- AML

| | Yıl | Tür | N° pts | IFDs | insidans% |
|---|---|---|---|---|---|
| **RCT** | | | | | |
| Cornelly et al, NEJM 2007 | 2002-05 | RCT | 304 | 7 | 2% |
| **“Real life” series** | | | | | |
| Michallet et al, Med Mycol 2011 | 2007-08 | Pros | 55 | 2 | 3.6% |
| Candoni et al, EHA 2011 | 2009-10 | Retro | 55 | 2 | 4% |
| Lerolle et al, ICAAC 2011 | 2007-10 | Retro | 209 | 8 | 3.8% |
| Hahn et al, Mycoses 2011 | 2007-08 | Retro | 21 | 1 | 5% |
| Egerer et al, Mycoses 2011 | 2007-09 | Retro | 76 | 1 | 1.3% |
| Vehreschild et al, JAC 2010 | 2006-08 | Retro | 77 | 3 | 3.9% |
| Busca et al, 5$^{th}$ TIMM 2011 | 2009-10 | Retro | 61 | 0 | 0 |
| Ananda-Rajah, Haematol 2012 | 2006-10 | Retro | 68 | 0 | 0 |
| Peterson et al, Mycoses 2013 | 2006-10 | Retro | 100 | 4 | 4% |
| ***TÜM ÇALIŞMALAR*** | | | **722** | **21** | **2.9%** |

# IDSA guidelines: 2010 update



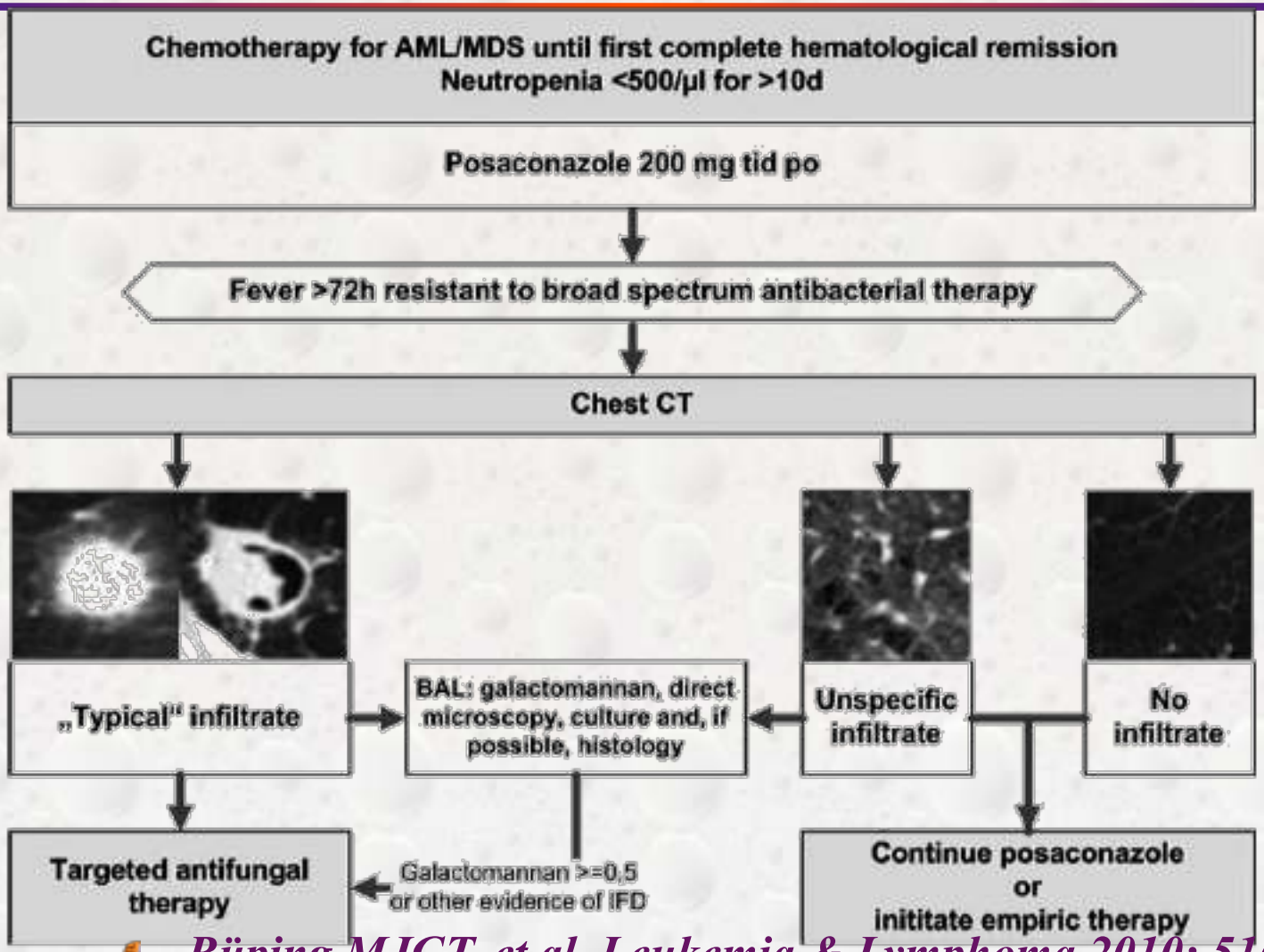

Freifeld et al, Clin Infect dis 2011




[1]If the patient was on prophylaxis with micafungin probably there is some contraindication for the use of triazoles.
[2]If the patient meets criteria of severe sepsis (signs of poor peripheral perfusion or functional failure of an organ), it is necessary that antifungal treatment should be effective as soon possible. Up to 20% of patients treated with voriconazole, optimal serum concentrations during the first week of treatment are not reached, so that initial treatment may include the association of voriconazole and liposomal amphotericin B or liposomal amphotericin B as monotherapy.
[3]If the AGA test is unavailable or negative, liposomal amphotericin B should be used. Caspofungin is an alternative option for cases in which the recommended regimens of choice cannot be used. Its activity and clinical efficacy against filamentous fungi are lower than those of triazoles and polyenes.

Figure 5 | Selection of early antifungal treatment

# Fever in neutropenic patients on posaconazole prophylaxis



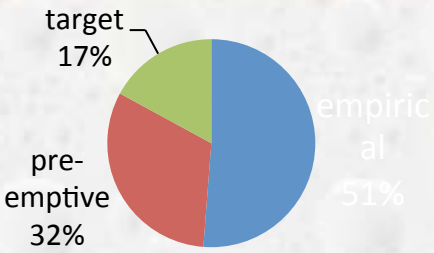

*Rüping MJGT, et al. Leukemia & Lymphoma 2010; 51(1): 20-26*

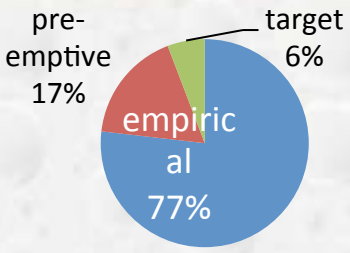
# Secondary endpoints

Posaconazole prophylaxis was also able to reduce:

- possible IFDs
- short term overall mortality
- the need of subsequent i.v. antifungal therapies

| | ITRA N°93 | POSA N°260 | p-value |
|---|---|---|---|
| Frontline antifungal approach | 41 (45.1%) | 69 (26.6%) | 0.001 |
| • Empirical | 21 (22.6%) | 53 (20.3%) | 0.49 |
| • Pre-emptive | 13 (14%) | 12 (4.6%) | 0.003 |
| • Target | 7 (7%) | 4 (1.5%) | 0.004 |



START

# The ideal story


Real life Clinical practice

Randomized Clinical Trials

Guidelines

PAGANO

START

RESTART

**The true story**

***Randomized Clinical Trials***

***Guidelines***

***Real life Clinical practice***

*PAGANO*

# Ampirik Antifungal Tedavi - SONUÇLAR

- Ampirik antifungal tedavi , yetersiz ve standardize olmayan erken tanı nedeniyle hala yaygın kabul gören bir yaklaşım
- Antifungal tedavi persistan ateşin 3-7. gününde başlanmalı
- Hem IFI, hem toksisite risk stratifikasyonu yapılmalı
- Çeşitli seçenekler arasında seçilecek ilaç; öngörülen toksisite, hasta uyumu, ilaç etkileşimleri, ilaç uygulama fiyatı


Teşekkürler…