PROS & CONS:
ANTIFUNGAL PROPHYLAXIS TO ALL HIGH RISK PATIENTS

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Clinical Research Unit
THE THREAT
THE INNOCENT VICTIM - THE PATIENT
THE DISEASE
PROPHYLAXIS
THE TREATMENT
# MORTALITY IN CANCER PATIENTS

<table>
<thead>
<tr>
<th>Reason</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial or Fungal Infection</td>
<td>35</td>
</tr>
<tr>
<td>Bleeding and Infection</td>
<td>27</td>
</tr>
<tr>
<td>Other (mainly metabolic)</td>
<td>29</td>
</tr>
<tr>
<td>Progression of the cancer</td>
<td>18</td>
</tr>
</tbody>
</table>
Epidemiology of sepsis in USA 1979-2000

Invasive Fungal Infections in Hematological Patients

- Aspergillus spp.
- Other mold
- Candida spp.
- Other yeast
- All fungal infections

n=538 IFI

THERE IS A THREAT!
From what?
Really dangerous?

WHO IS THE INNOCENT VICTIM? (High risk patient)

HOW CAN WE DO THE PROPHYLAXIS?

WHAT HAPPENS IF WE DO NOT PROPHYLAXIS? (The cost of the disease)
THE THREAT
1980

Candida

Invasive candida
Non C. albicans > 70.6%

1990

Hyalohyphomycetes 9%
Fusarium spp
Scedosporium apiospermum

Mucorales
Phaeohyphomycetes
And other mold 10%

2000

Aspergillus: 69%
A. fumigatus 56%
Other 18%
A. flavus 11%
A. niger 9%
A. terreus 6%
Candida spp. distribution before 2006 in AU Hematology Dept.

<table>
<thead>
<tr>
<th>Year</th>
<th>Candida albicans</th>
<th>Non Albicanders Candida</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>82</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>2003</td>
<td>69</td>
<td>73</td>
<td>3</td>
</tr>
<tr>
<td>2004</td>
<td>101</td>
<td>103</td>
<td>19</td>
</tr>
<tr>
<td>2005</td>
<td>96</td>
<td>118</td>
<td>19</td>
</tr>
<tr>
<td>2006</td>
<td>138</td>
<td>127</td>
<td>17</td>
</tr>
</tbody>
</table>
Candida spp. distribution after 2006 AU Hematology Dept.

Gülden YILMAZ et al.
### Table 2

Underlying pathology/medical care of patients with candidaemia (n = 2089; more than one may be present in each episode)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>1007</td>
<td>48.2</td>
</tr>
<tr>
<td>Intensive care</td>
<td>839</td>
<td>40.2</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>471</td>
<td>22.5</td>
</tr>
<tr>
<td>Steroids</td>
<td>364</td>
<td>17.4</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>257</td>
<td>12.3</td>
</tr>
<tr>
<td>Premature birth</td>
<td>125</td>
<td>6.0</td>
</tr>
<tr>
<td>HIV infection</td>
<td>63</td>
<td>3.0</td>
</tr>
<tr>
<td>Burns</td>
<td>29</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Underlying Disease in Invasive Aspergillosis

595 patients
Change in invasive moulds

Emergence of fusarioses in a university hospital in Turkey during a 20-year period

B. Dalyan Cilo¹ · A. M. S. Al-Hatmi²,³,⁴ · S. Seyedmousavi⁵,⁶,⁷,⁸,⁹ · A. J. M. M. Rijs¹⁰ · P. E. Verweij¹⁰ · B. Ener¹ · G. S. de Hoog²,⁳,⁵,⁶,⁷,⁸,⁹ · A. D. van Diepeningen³

Received: 26 March 2015 / Accepted: 5 May 2015

Fig. 1  Increasing incidence of *Fusarium* infections over the past 20 years in the studied university hospital in Turkey
Incidence of IFI in different hematological malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>IFD incidence (%)</th>
<th>Mold (%)</th>
<th>Yeast (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>12.3</td>
<td>7.9</td>
<td>4.4</td>
</tr>
<tr>
<td>ALL</td>
<td>6.5</td>
<td>4.3</td>
<td>2.2</td>
</tr>
<tr>
<td>CML</td>
<td>2.5</td>
<td>2.3</td>
<td>0.2</td>
</tr>
<tr>
<td>CLL</td>
<td>0.5</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>NHL</td>
<td>1.6</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>HD</td>
<td>0.7</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>MM</td>
<td>0.5</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Mold: 90% *Aspergillus spp*, 4% *Zygomycetes*, 4% *Fusarium*

Yeast: *Candida spp* 90%, *Cryptococcus spp* 4%, *Trichosporon* 4%

N = 11.802
A Double-Blind, Multicentre, Randomised, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Prophylactic Liposomal Amphotericin B (AmBisome®) for the Prevention of Invasive Fungal Infections in Subjects Receiving Remission-Induction Chemotherapy for Acute Lymphoblastic Leukaemia (AmBiGuard trial)

7.9% (18/228) subjects in the L-AMB group and 11.7% (13/111) subjects in the placebo group were considered by the IDRB to have experienced a proven or probable IFI (p=0.24, RR 0.33 [CI -0.32 to 0.66]). Of these, 1 case (0.4%) in the L-
WHY NUMBERS?

- If the prevalence is 2%, to reduce it by 50%, you need to prophylaxis 100 patients,

- If the prevalence is 4.5%, to reduce it by 50%, you need to prophylaxis 44 patients,

........................
<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Incidence rates, %</th>
<th>Fluconazole (400 mg QD) or itraconazole (200 mg BID)</th>
<th>Relative risk reduction&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Absolute risk reduction&lt;sup&gt;d&lt;/sup&gt;</th>
<th>NNT&lt;sup&gt;°&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive fungal infection</td>
<td>2.3</td>
<td>8.4</td>
<td>0.73</td>
<td>0.061</td>
<td>16</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>0.7</td>
<td>6.7</td>
<td>0.9</td>
<td>0.061</td>
<td>17</td>
</tr>
<tr>
<td>Death due to fungal infection</td>
<td>1.6</td>
<td>5.4</td>
<td>0.69</td>
<td>0.037</td>
<td>27</td>
</tr>
<tr>
<td>Death due to any cause</td>
<td>14.5</td>
<td>21.5</td>
<td>0.33</td>
<td>0.07</td>
<td>14</td>
</tr>
</tbody>
</table>

Invasive Fungal Infections in USA
Transnet Data - 875 HSCT
CID 2010

Distribution

- Aspergilosis: 21%
- Candidiasis: 43%
- Zygomycosis: 8%
- Other: 28%

IFI Incidence

- MUR: 7.7%
- MR: 5.8%
- MMR: 8.1%
- AUT: 1.2%
Aspergillosis related mortality - SCT

Aspergillosis after ASCT, 1993-1998

Marr KA, et al. Blood 2002;100:4358
Mortality in ASCT

- Aspergillus: 74.6%
- Candida: 65.4%
- Fusarium: 93.7%
- Zygomycosis: 72%
Mortality in Candidemia (12 weeks) - PATH

### INSIDANCE (%)

<table>
<thead>
<tr>
<th></th>
<th>Aspergillus</th>
<th>Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic SCT</td>
<td>2.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Autologous SCT</td>
<td>0.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* (Except MDS, aplastic anemia and HSCT)

**Pagano L, Haematologica 2006; 91(8):1068-73**

**Pagano L, CID 2007:45 (1):1161-1170**

### MORTALITY (%)

<table>
<thead>
<tr>
<th></th>
<th>Aspergillus</th>
<th>Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic SCT</td>
<td>77.2</td>
<td>57.1</td>
</tr>
<tr>
<td>Autologous SCT</td>
<td>40</td>
<td>43.8</td>
</tr>
</tbody>
</table>
Autopsy and IFI in Leukemia and HSCT patients


77% of the mortality is related to IFI

327 Autopsy

IFI in Autopsy

Premortem IFI

Postmortem IFI

74.8%

25.2%

30.3%
The vanishing “gold standard”

Hematology Patient Autopsy Rate Over 20 Year Period (MDACC)

P<0.001
Chi-square Trend

Autopsies per 100 Deaths

1989-1993
1994-1998
1999-2003
2004-2008
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we’ve been waiting for?
USUAL SUSPECTS

- Anti-TNF Treatment
- Rituximab
- Alemtuzumab
RITUXIMAB and ALEMTUZUMAB

- Rituximab have an impact on fungal infections when used together with corticosteroids and purine analogs.

- Increasing Aspergillus, Candida, and PJP with alemtuzumab? Neutropenia and corticosteroid use are main determinants.
Risk for Invasive Aspergillosis Based on Primary Host Factor

HIGH RISK
- Allogeneic HSCT with graft versus host disease
- AML/MDS treated with remission-induction chemotherapy
- Lung or heart transplantation
- Small-bowel transplantation
- Liver transplantation
- Allogeneic HSCT without graft versus host disease
- Acute myeloblastic leukemia during consolidation phase
- Acute lymphoblastic leukemia
- Heart transplantation
- Chronic lymphocytic leukemia
- Myelodysplastic syndrome
- Multiple myeloma
- COPD with acute exacerbation
- AIDS
- Non-Hodgkin’s lymphoma
- Autologous HSCT
- Kidney transplantation
- Solid tumor
- Autoimmune disorder

INTERMEDIATE RISK

LOW RISK
- Kidney transplantation
- Solid tumor
- Autoimmune disorder

ACUTE LEUKEMIA - MDS

Chemotherapy
Prophylaxis
Neutropenia

Chemotherapy
Prophylaxis
Neutropenia

Chemotherapy
Prophylaxis
Neutropenia

Allogeneic SCT

Chemotherapy
Fluconazole
Neutropenia

Prophylaxis

GVHD

© by author
ANC (cells/mm³)

500

Chemotherapy

HSCT

Engraftment

GVHD + Immunosuppressive Therapy

Fluconazole

Goodman et al 1992; Slavin et al 1995

Itraconazole

Marr et al 2004

Micafungin

van Burik et al 2004

Posaconazole

Cornely et al 2007

Posaconazole

Ullmann et al 2007

Voriconazole

Wingard et al 2010

Voriconazole

Marks et al 2011
Prospective, controlled studies on primary antifungal prophylaxis in allogeneic HSCT over the last 10 years

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Duration of Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole versus fluconazole</td>
<td>Until 180 days after allo SCT, or until 4 weeks after discontinuation of GvHD therapy</td>
</tr>
<tr>
<td>Marr KA et al. Blood 2004</td>
<td></td>
</tr>
<tr>
<td>Micafungin versus fluconazole</td>
<td>Allogeneic and autologous HSCT only pre-engraftment</td>
</tr>
<tr>
<td>Posaconazole versus fluconazole</td>
<td>Allogeneic HSCT only during GvHD</td>
</tr>
<tr>
<td>Ullmann A et al. NEJM 2007</td>
<td></td>
</tr>
<tr>
<td>Voriconazole versus fluconazole</td>
<td>Allogeneic HSCT until 100 days or until 180 days if GvHD</td>
</tr>
<tr>
<td>Wingard JR et al. Blood 2010</td>
<td></td>
</tr>
<tr>
<td>Voriconazole versus itraconazole</td>
<td>Allogeneic HSCT until 100 days or until 180 days if GvHD</td>
</tr>
</tbody>
</table>
Prophylaxis can save lives in high risk hematology patients: Fluconazole

Goodman et al: 52% Allografts/48% Auto, Flu (400 mg/d) vs Placebo until Engraftment

Slavin et al: 88% Allografts/12% Auto, Flu (400 mg/d) vs Placebo until Day 75

*Statistical significance between fluconazole and placebo.
Fluconazole in Stem Cell Transplantation

Related and Unrelated Donor Transplant

Survival Probability

Years After Transplant

P = .0018

Micafungin in Stem Cell Transplantation

Posaconazole in AML

Posaconazole in Stem Cell Transplantation (CGVHD)

Antifungal Prophylaxis in AML/MDS
A 12-year Experience: Royal Melbourne Hospital

- 261 patients/753 courses prophylaxis
- Breakthrough IFI (prov/susp/poss)
  - Posa/Vori: 8%
  - Flu/Itra: 20%
- Posa/Vori significant reductions in:
  - Premature discontinuations: 46% vs 22% (p <0.001)
  - Empirical treatment: 31% vs 8.5% (p <0.001)
- Posa fewer courses requiring CT:
  - 43% vs 26% (p <0.001)
- Posa prophylaxis NNT=6
- Microbiological infections moulds
- Resistance uncommon

Flu (57) Itra (59) Vori (82) Posa (68)

# Recommendations (2013)

## Acute myeloid leukaemia patients undergoing intensive chemotherapy

<table>
<thead>
<tr>
<th>Antifungal drug</th>
<th>Grading</th>
<th>Comments</th>
<th>Alarms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole (400 mg q24)</td>
<td>BI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole oral solution</td>
<td>BI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.5 mg/kg q12h.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole (oral solution</td>
<td>AI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg q8h or tablet 300 mg q24h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>following a loading dose of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg q12h on day 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole (200 mg q12h)</td>
<td>BII</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aloes should not be used empirically in case of prior mould-active azole prophylaxis.
# Recommendations for allogeneic HSCT recipients (2013)

<table>
<thead>
<tr>
<th>Antifungal prophylaxis*</th>
<th>Pre-engraftment Low risk for moulds</th>
<th>Pre-engraftment High risk for moulds</th>
<th>GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>A-I</td>
<td>A-III - against</td>
<td>A-III against</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>B-I</td>
<td>B-I</td>
<td>B-I</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>B-I</td>
<td>B-I</td>
<td>B-1</td>
</tr>
<tr>
<td>Posaconazole OS/Tablet</td>
<td>B-II</td>
<td>B-II</td>
<td>A-I</td>
</tr>
<tr>
<td>Micafungin</td>
<td>B-I</td>
<td>C-I</td>
<td>C-II</td>
</tr>
<tr>
<td>Caspofungin /anidulafungin</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>C-II</td>
<td>C-II</td>
<td>C-II</td>
</tr>
<tr>
<td>Aerosolized amphotericin B plus fluconazole</td>
<td>C-III</td>
<td>B-II</td>
<td>No data</td>
</tr>
</tbody>
</table>

*For doses & need for Therapeutic Drug Monitoring: please refer to slides 21 and 22
THE COST
Resistance in Aspergillus
First Determination of Azole Resistance in Aspergillus fumigatus Strains Carrying the TR34/L98H Mutations in Turkey

Gülşah Ecen Özmertören, Seçil Ak, Beyza Ener, Harun Agca, Burcu Dalyan Cilo, Berrin Tunca

Journal of Infection and Chemotherapy 05/2015; DOI: 10.1016/j.jiac.2015.04.012

ABSTRACT Aspergillus fumigatus is the most important etiological agent of invasive aspergillosis. Recently, an increasing number of azole-resistant A. fumigatus isolates have been described in various countries. The prevalence of azole resistance was investigated in this study using our culture collection of A. fumigatus isolates collected between 1999 and 2012 from clinical specimens. Seven hundred and forty-six A. fumigatus isolates, collected from 419 patients, were investigated. First, all isolates were screened for resistance to itraconazole by subculturing on Sabouraud dextrose agar that contained 4 mg/L itraconazole. For isolates that grew on the itraconazole containing agar, the in vitro activities of amphotericin B, itraconazole, voriconazole and posaconazole were determined using the Clinical and Laboratory Standards Institute (CLSI) M38-A reference method. After PCR amplification, the full sequence of the cyp51A gene and its promoter region was determined for all in vitro azole-resistant isolates. Itraconazole resistance was found in 10.2% of the A. fumigatus isolates. From 2000 onwards, patients were observed annually with an itraconazole-resistant isolate. According to in vitro susceptibility tests, amphotericin B exhibited good activity against all
Environmental azole-resistant *A. fumigatus* in Germany

Netherlands
France
Denmark
China
India
Great Britain
Germany
Turkey

Abstract

Azole antifungal drug resistance in *Aspergillus fumigatus* is an emerging problem in several parts of the world. Here we have investigated the distribution of such strains in soils from Germany. In a general positivity rate of 12%, most prevalently we found strains with the TR34/L98H and TR46/Y121F/T289A alleles, dispersed along a corridor across Northern Germany. Comparison of the distribution of resistance alleles and genotypes between environment and clinical samples suggests local clinical clusters.

Copyright © 2015, American Society for Microbiology. All Rights Reserved.
Antifungal Prophylaxis in AML/MDS
A 12-year Experience: Royal Melbourne Hospital

**Breakthrough Invasive Fungal Infections**

- 261 patients/753 courses prophylaxis
- Breakthrough IFI (prov/prov/poss)
  - Posa/Vori: 8%
  - Flu/Itra: 20%

  Posa/Vori significant reductions in:
  - Premature discontinuations: 46% vs 22% (p <0.001)
  - Empirical treatment: 31% vs 8.5% (p <0.001)
  - Posa fewer courses requiring CT:
    - 43% vs 26% (p <0.001)
  - Posa prophylaxis NNT=6
  - Microbiological infections moulds
  - Resistance uncommon

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Anada-Rajah MR et al. *Haematologica* 2012;97:459-63
Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective anti-mold prophylaxis.

Duarte RF, Sánchez-Ortega I, Cuesta I, Arman M, Patiño B, Fernández de Sevilla A, Gudiel C, Ayats J, Cuence Estrella M.

Abstract

BACKGROUND: There is a practical need to investigate the performance of the serum galactomannan (GM) assay in hematology patients with a potentially low pre-test risk of invasive aspergillosis following effective anti-mold prophylaxis.

METHODS: We present a four-year study with 262 unselected consecutive high-risk episodes, prospectively managed with posaconazole primary prophylaxis and a uniform diagnostic algorithm, including biweekly serum GM quantification for early detection of invasive aspergillosis.

RESULTS: 2972 serum GM tests were performed (median 11 per episode, 3-30); the vast majority was negative (96.7% tests; 83.6% episodes). The incidence of breakthrough invasive aspergillosis was 1.9% (5/262), all with true positive GM test results. Our study identified 30 false positive GM evaluable episodes (85.7%, 13.8% of all evaluable episodes), validating with real-life data the low positive predictive value of the assay in this setting (12%). In 26 out of these 30 episodes (86.7%), the false positive result/s occurred in tests performed as preemptive surveillance only. Conversely, in evaluable cases with positive GM tests and a clinical suspicion of invasive fungal disease, the performance of diagnostic-driven GM tests improved, with a positive predictive value of 89.6%.

CONCLUSIONS: The low pre-test risk of invasive aspergillosis in the context of effective anti-mold prophylaxis renders serum GM surveillance of asymptomatic patients unreliable, as all results would be either negative or false positive. The test remains useful to diagnose patients with a clinical suspicion of invasive fungal disease, calling for a more efficient co-positioning of effective prophylaxis and GM testing in this clinical setting.
The impact of Azole resistance in clinical setting

Azole resistance in 2/58 of the deceased patients
IV Antifungal costs

France, Italy, Germany, Spain, UK (2001-2004)

Ref: EU IMS Data
Treatment cost development of patients undergoing remission induction chemotherapy: a pharmacoeconomic analysis before and after introduction of posaconazole prophylaxis

Sebastian M. Heimann,1 Oliver A. Cornely,1,2,3,4,5 Maria J. G. T. Vehreschild,1,5 Jan Glossmann,1,3 Matthias Kochanek,1 Karl-Anton Kreuzer,1,3 Michael Hallek1,3,4 and Jörg J. Vehreschild1,5

11st Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany, 2Clinical Trials Centre Cologne, ZKS Köln, University Hospital of Cologne, Cologne, Germany, 3Center for Integrated Oncology Köln Bonn, CIO Köln Bonn, University Hospital of Cologne, Cologne, Germany, 4Cluster of Excellence – Cellular Stress Responses in Aging-Associated Diseases, CECAD, University Hospital of Cologne, Cologne, Germany and 5German Centre for Infection Research (DZIF), partner site Bonn-Cologne, Cologne, Germany

Summary

Prior clinical trials have demonstrated efficacy and effectiveness of posaconazole in the prophylaxis of invasive fungal diseases in high-risk patients. Controversy exists about the cost-effectiveness of this approach. We performed an analysis comparing the direct costs of posaconazole prophylaxis against polyene mouthwash (thrush) prophylaxis in patients with acute myelogenous leukaemia (AML). Data of AML patients receiving remission-induction chemotherapy were extracted from the CoCoNut (Cologne Cohort of Neutropenic Patients) database to compare hospital costs of patients before (2003–2005) and after (2006–2008) introduction of posaconazole prophylaxis. Treatment on general ward, intensive care unit (ICU), mechanical ventilation, diagnostic procedures, and all anti-infectives were calculated. Patient groups were well matched according to age, gender and duration of neutropenia. The mean costs per patient in the posaconazole group (n = 76) and the polyene mouthwash group (n = 81) were €21 040 (95% confidence interval (CI): €18 204–€23 876) and €23 169 (95% CI: €19 402–€26 937) per patient. Antifungal treatment costs were €4580 (95% CI: €3678–€5482) and €4019 (95% CI: €2825–€5214). Duration on the ICU was 2582 (95% CI: 984.1–4181.7) and 5517 (95% CI: 2206–8827.3) min. In our hospital, primary antifungal prophylaxis by posaconazole was cost-effective. There was a trend towards cost savings, which was primarily caused by a shorter overall length of stay and the less frequent ICU treatment.
Do novel diagnostic tools help us improving survival?

Use of AF Treatment (% & days)

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Empirical</th>
<th>Preemptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (%)</td>
<td>97.3%</td>
<td>95.1%</td>
</tr>
<tr>
<td>p-value</td>
<td>.31</td>
<td>.97</td>
</tr>
</tbody>
</table>

Use of AF (%)

<table>
<thead>
<tr>
<th></th>
<th>Empirical</th>
<th>Preemptive</th>
</tr>
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<tbody>
<tr>
<td>61.3%</td>
<td>39.2%</td>
<td></td>
</tr>
</tbody>
</table>

Days of AF (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Empirical</th>
<th>Preemptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 ± 7.2</td>
<td>7.0 ± 8.5</td>
<td></td>
</tr>
</tbody>
</table>

p-values:

- p < .001
- p < .01
- p = .31
Secondary antifungal prophylaxis

- **Condition:**
  - Previously documented and fully resolved IFI plus
  - A new episode of
    - prolonged neutropenia (usually chemotherapy-induced)
    - severe immunosuppression (usually transplantation)

- **Recommendation:** All

- No drug-specific recommendations possible, but choice should be based on the causative fungal pathogen of the previous IFI and the response to antifungal agents during that episode
Managing of the fungal infections in cancer patients is a matter of a dedicated team!

Thank you...