PRE-EMPTIVE VS. EMPIRICAL TREATMENT

Omrum Uzun
Hacettepe University, Faculty of Medicine, Section of Infectious Diseases
EMPIRICAL ANTIFUNGAL THERAPY: CLINICAL RATIONALE

- High Incidence of IFI.
  
  Allo-HSCT (5–30%) > Acute leukemia (5-15%) > Auto- SCT ~ 4%

- Better response to antineoplastic chemotherapy and increased survival rates.

- Difficult or delayed diagnosis.

- High morbidity / mortality with established infection.
FEVER-DRIVEN APPROACH
EMPIRICAL ANTIFUNGAL RX: NCI TRIAL
PIZZO ET AL. AM J MED 1982;72:101

Febrile on Day 7 of AB Rx (n=50)

- AB d/c (n=16)
- AB continued (n=16)
- + 0.5 mg/kg/d AmB-d (n=18)

Defervescence, day

11 8 6
Febrile on Day 7 of AB Rx
(n=50)

- AB d/c (n=16)
  - 6%
  - Aspergillosis (1)

- AB continued (n=16)
  - 36%
  - Aspergillosis (1)
  - Mixed (1)
  - Candidiasis (1)

- + 0.5 mg/kg/d AmB-d (n=18)
  - 6%
  - P. boydii (1)
<table>
<thead>
<tr>
<th>Response, %</th>
<th>AmB-d* (n=68)</th>
<th>Control (n=64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69</td>
<td>53</td>
<td>.09</td>
</tr>
</tbody>
</table>
WHICH AGENT FOR EMPIRIC THERAPY?

Membrane Function
Polyenes
AmB-d
L-AmB
ABLC
ABCD

Azoles
Itraconazole
Voriconazole

Cell Wall Synthesis
Candins
Caspofungin

Nucleic Acid Synthesis
Pyrimidine analog
LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL THERAPY IN PATIENTS WITH PERSISTENT FEVER AND NEUTROPENIA

THOMAS J. WALSH, M.D., ROBERT W. FINBERG, M.D., CAROLA ARNDT, M.D., JOHN HIEMENZ, M.D., CINDY SCHWARTZ, M.D., DAVID BODENSTEINER, M.D., PETER PAPPAS, M.D., NITA SEIBEL, M.D., RICHARD N. GREENBERG, M.D., STEPHEN DUMMER, M.D., MINDY SCHUSTER, M.D., AND JOHN S. HOLCENBERG, M.D., FOR THE NATIONAL INSTITUTE OF ALLERGY AND INFECTION DISEASES MYCOSES STUDY GROUP*
OVERALL RESPONSE

PREVENTION OF IFI UNDER RX

>7 DAY SURVIVAL AFTER RX

NO PREMATURE D/C OF RX

DEFERVESCENCE DURING NP

RESPONSE IN PTS WITH IFI

L-AmB

VRC

MSG 2002
OVERALL RESPONSE
PREVENTION OF IFI UNDER RX
>7 DAY SURVIVAL AFTER RX
NO PREMATURE D/C OF RX
DEFERVESCENCE DURING NP
RESPONSE IN PTS WITH IFI
**Empirical Antifungal Rx: EORTC Trial**

Meunier F. Am J Med 1989; 86: 668

<table>
<thead>
<tr>
<th>Response, %</th>
<th>AmB-d* (n=68)</th>
<th>Control (n=64)</th>
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</thead>
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<tr>
<td></td>
<td>69</td>
<td>53</td>
<td>.09</td>
</tr>
</tbody>
</table>
Not all neutropenic patients persistently febrile under antibiotics are the same!

DETERMINE RISK CATEGORY
EMPIRICAL APPROACH: DETERMINE RISK CATEGORY

**EXPOSURE**
- History of IA
- Environmental exposure
- Colonization (?)

**NET STATE OF IMMUNOSUPPRESSION**
- Baseline immunity
- Chemotherapy
- Cancer status
- CD4 count
- Number of stem cells infused
EMPIRICAL APPROACH: DETERMINE RISK CATEGORY

- ORGAN DYSFUNCTION
  - Renal insufficiency
  - Pulmonary dysfunction
  - GVHD

- OTHER
  - Age
  - Concomitant disease
  - Mould-active prophylaxis
“FEVER-DRIVEN’’ THERAPY

Early treatment of IFI? Prophylaxis?
"I stopped taking the medicine because I prefer the original disease to the side effects."

"It’s not us, Louis. It’s our medications that don’t interact well together."
IS FEVER OBJECTIVE PARAMETER?

From B. de Pauw
IS FEVER OBJECTIVE PARAMETER?

INFLUENCED BY ANTIPYRETICS

NOT INFECTION-SPECIFIC

NOT LIKELY TO SUBSIDE RAPIDLY

From B. de Pauw
CLUES FOR IA

- Clinical
- Radiological
- Non-culture based microbiological
CLINICAL SIGNS OF INVASIVE ASPERGILLOSIS

Cornillet A, et al. CID 2006;43:577
# Scoring for IPA in Patients with Leukemia


<table>
<thead>
<tr>
<th></th>
<th>Control (Score=0)</th>
<th>Case (Score=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of febrile neutropenia</td>
<td>&lt;22</td>
<td>≥30</td>
</tr>
<tr>
<td>Days of FUO</td>
<td>0</td>
<td>≥2</td>
</tr>
<tr>
<td>Febrile days</td>
<td>&lt; 6</td>
<td>≥14</td>
</tr>
<tr>
<td>Febrile days under antibiotic Rx</td>
<td>&lt;13</td>
<td>≥19</td>
</tr>
<tr>
<td>T at admission (°F)</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Rales without hypervolemia</td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>Nasal/sinus findings in PE</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Pleuretic chest pain</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Infiltrates in CXR</td>
<td>absent/ one lobe</td>
<td>multilobar</td>
</tr>
<tr>
<td>Day of infiltrate</td>
<td>before day 7</td>
<td>after day 14</td>
</tr>
<tr>
<td>Cavity /nodules in CXR</td>
<td>present</td>
<td>absent</td>
</tr>
</tbody>
</table>
Scoring for IPA in Patients with Leukemia


I: definite (histopath. +)
II: “probable” case
   (infiltrate + nasal/sputum culture
    nasal ulcer (necrosis + histopath/culture)
IIIa: "unknown"
   (pulmonary infiltrate)
IIIb: “unknown”
   (febrile >7 days /nasal culture)
IV: “probable” control
   (none of 1-IIIb criteria)
V: control
   (tests and autopsy negative)
### VALIDATION (RETROSPECTIVE)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: definite</td>
<td>Histopath. (+)</td>
</tr>
<tr>
<td>II: “probable” case</td>
<td>Infiltrate + nasal/sputum culture, nasal ulcer (necrosis + histopath/culture)</td>
</tr>
<tr>
<td>IIIa: “unknown”</td>
<td>Pulmonary infiltrate</td>
</tr>
<tr>
<td>IIIb: “unknown”</td>
<td>Febrile &gt;7 days /nasal culture</td>
</tr>
<tr>
<td>IV: “probable” control</td>
<td>None of I-IIIb criteria</td>
</tr>
<tr>
<td>V: control</td>
<td>Tests and autopsy negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>92.8</td>
<td>98.3</td>
<td>92.8</td>
<td>98.3</td>
</tr>
</tbody>
</table>
VALIDATION (RETROSPECTIVE)

I: definite (histopath. +)
II: “probable” case
   (infiltrate + nasal/sputum culture
   nasal ulcer (necrosis + histopath/ 
culture)
IIIa: “unknown”
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   (none of I-IIIb criteria)
V: control
   (tests and autopsy negative)

<table>
<thead>
<tr>
<th></th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92.8</td>
<td>87.5</td>
<td>56.5</td>
<td>98.6</td>
</tr>
</tbody>
</table>
IMAGING CLUES
EARLY CXR AND CT IN IPA
53 persistently febrile neutropenic patients
21 diagnosed with IPA later.

- Halo sign (20)
- Nodule with subsequent cavitation (5)
- Segmental consolidation surrounded with ground-glass appearance (1)

29% normal
71% nonspecific

100% abnormal
CT FINDINGS IN IPA

SYSTEMATIC CT IN DX OF IPA

Days to Dx
- Since admission
- Since first suspicion
- Halo sign in CT

<table>
<thead>
<tr>
<th></th>
<th>Systematic CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior</td>
<td>31 ± 9</td>
</tr>
<tr>
<td>After</td>
<td>21 ± 5</td>
</tr>
<tr>
<td></td>
<td>7 ± 5</td>
</tr>
<tr>
<td></td>
<td>2 ± 1</td>
</tr>
<tr>
<td></td>
<td>1/8</td>
</tr>
<tr>
<td></td>
<td>23/25</td>
</tr>
</tbody>
</table>
NON-CULTURE BASED CLUES
GALACTOMANNAN AS SURROGATE MARKER: AUTOPSY STUDY

TIMING OF GM (+) IN ALLO-HSCT
MAERTENS ET AL. JID 2002;186:1297.

GM CT CXR culture
6 days 2 days 1 day
<table>
<thead>
<tr>
<th>ODI</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>78% (61%-89%)</td>
<td>81% (72%-88%)</td>
</tr>
<tr>
<td>1.0</td>
<td>75% (59%-86%)</td>
<td>91% (84%-95%)</td>
</tr>
<tr>
<td>1.5</td>
<td>64% (50%-77%)</td>
<td>95% (91%-97%)</td>
</tr>
</tbody>
</table>
IMPACT OF ANTIFUNGAL RX ON GM ASSAY

A

Index cutoff value, 1.5
Index cutoff value, 1
Index cutoff value, 0.5

Sensitivity

Time relative to diagnosis, days

No Rx

B

Index cutoff value, 1.5
Index cutoff value, 1
Index cutoff value, 0.5

Rx (+)
GM IN BAL VS SERUM GM AND BG IN ICU
Acosta et al. CMI 2011;7:1073

proven+probable, n=9
proven, n=4
all IA +PCP, n=13

**FIG. 1.** Area under the curve (AUC) of receiver-operating curves (ROC) for: (a) all invasive aspergillosis (IA) cases, proven and probable; (b) proven IA cases; and (c) all invasive fungal disease cases (IA and *P. jirovecii* pneumonia). In case of IA (proven and probable), the AUC for GM in BAL was significantly higher than GM and BG in serum (p 0.0258 and p 0.0322, respectively). In cases of proven IA, there was no significant difference between the AUC for GM in BAL when compared with the AUC for GM and BG in serum (p 0.203 and p 0.159, respectively).
GM IN BAL FLUID: BIVARIATE META-ANALYSIS

<table>
<thead>
<tr>
<th>Studies</th>
<th>No. Studies</th>
<th>Pooled SEN (95% CI)</th>
<th>Pooled SPE (95% CI)</th>
<th>Pooled PLR (95% CI)</th>
<th>Pooled NLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analyses</td>
<td>13</td>
<td>0.90 (0.79-0.96)</td>
<td>0.94 (0.90-0.96)</td>
<td>14.87 (8.89-24.90)</td>
<td>0.10 (0.04-0.24)</td>
</tr>
<tr>
<td>Cutoff of 0.5 for positivity</td>
<td>8</td>
<td>0.86 (0.70-0.94)</td>
<td>0.89 (0.85-0.92)</td>
<td>7.69 (5.75-10.28)</td>
<td>0.15 (0.07-0.35)</td>
</tr>
<tr>
<td><strong>Cutoff of 1 for positivity</strong></td>
<td>11</td>
<td><strong>0.85 (0.72-0.93)</strong></td>
<td><strong>0.94 (0.89-0.97)</strong></td>
<td><strong>14.29 (8.33-24.50)</strong></td>
<td><strong>0.16 (0.08-0.31)</strong></td>
</tr>
<tr>
<td>Cutoff of 1.5 for positivity</td>
<td>9</td>
<td>0.70 (0.49-0.85)</td>
<td>0.96 (0.93-0.98)</td>
<td>18.97 (10.93-32.93)</td>
<td>0.31 (0.17-0.57)</td>
</tr>
<tr>
<td>Cutoff of 2 for positivity</td>
<td>5</td>
<td>0.61 (0.38-0.80)</td>
<td>0.96 (0.92-0.98)</td>
<td>16.13 (8.07-32.25)</td>
<td>0.40 (0.23-0.70)</td>
</tr>
</tbody>
</table>
FUNGAL CELL WALL

- Mannoproteins
  - beta(1,6)-glucan
  - beta(1,3)-glucan
- Chitin
- Phospholipid bilayer of cell membrane

- glucan synthase inhibitor
- depletion of beta(1,3) glucans in cell wall
- Inhibition of beta(1,3) glucan synthase

"Horseshoe crab"
<table>
<thead>
<tr>
<th>Proven infection (n)</th>
<th>Positivity (cut-off: 60 pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis (107)</td>
<td>81.3%</td>
</tr>
<tr>
<td>Aspergillosis (10)</td>
<td>80%</td>
</tr>
<tr>
<td>Fusariosis (3)</td>
<td>3/3</td>
</tr>
<tr>
<td>Zygomycosis (3)</td>
<td>0</td>
</tr>
<tr>
<td>Cryptococcal inf. (12)</td>
<td>3/12</td>
</tr>
</tbody>
</table>
BETA-GLUCAN AS SURROGATE MARKER IN IA: AUTOPSY STUDY


Cut-off: 80 pg/mL

<table>
<thead>
<tr>
<th></th>
<th>n=14</th>
<th>n=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA (+)</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>IFI (-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sen. 85.7%
Spe. 36.4%
PPV 36.4%
NPV 85.7%
BETA-GLUCAN AS SURROGATE MARKER IN IA: AUTOPSY STUDY

Cut-off: 140 pg/mL

All patients with IA and (+) BG had (+) GM in BAL.
**Beta-glucan in DX: Meta-analysis**

Lamoth F, et al. CID 2011; Dec 23 *epub*

- **6 cohort studies**
- **1771 patients**
- **414 IFIs**
  - (214 proven + probable)

<table>
<thead>
<tr>
<th>Author</th>
<th>Brand</th>
<th>Recommended cutoff, (pg/mL)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odabasi (2004)</td>
<td>Fungitell</td>
<td>60</td>
<td>861.00 (48.68–15229.64)</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 71.6%, P = .007)</td>
<td></td>
<td>16.30 (6.52–40.76)</td>
</tr>
<tr>
<td>Kami (2000)</td>
<td>Fungitec G</td>
<td>20</td>
<td>140.52 (32.52–607.18)</td>
</tr>
<tr>
<td>Odabasi (2004)</td>
<td>Fungitell</td>
<td>60</td>
<td>103.33 (10.38–1028.64)</td>
</tr>
<tr>
<td>Kawazu (2004)</td>
<td>Wako/Maruha</td>
<td>11</td>
<td>74.67 (9.14–609.64)</td>
</tr>
<tr>
<td>Senn (2008)</td>
<td>Wako/Maruha</td>
<td>11</td>
<td>111.84 (38.59–324.15)</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%, P = .887)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Criterion A:** 1 single positive value  
**Criterion B:** 2 positive consecutive values
# PCR IN DX OF INVASIVE ASPERGILLOSIS

**META-ANALYSIS**


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<table>
<thead>
<tr>
<th></th>
<th>DOR (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>One PCR-positive sample</td>
<td>22.1 (7.7–62.9)</td>
<td>0.88 (0.75–0.94)</td>
<td>0.75 (0.63–0.84)</td>
<td>3.53</td>
</tr>
<tr>
<td>Two PCR-positive samples</td>
<td>21.3 (6.8–466.3)</td>
<td>0.75 (0.54–0.88)</td>
<td>0.87 (0.78–0.93)</td>
<td>6.04</td>
</tr>
</tbody>
</table>

**DOR** = diagnostic odds ratio.

**Table 3: Results of bivariate analyses**
### PCR ON BAL FLUID: BIVARIATE META-ANALYSIS


<table>
<thead>
<tr>
<th>Study Details</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 studies</td>
<td></td>
</tr>
<tr>
<td>1,191 at risk patients</td>
<td></td>
</tr>
<tr>
<td>Proven + probable vs possible + no IA</td>
<td></td>
</tr>
<tr>
<td>Diagnostic OR</td>
<td>122 (41-363)</td>
</tr>
<tr>
<td>Pooled sensitivity</td>
<td>0.91 (0.79-0.96)</td>
</tr>
<tr>
<td>Pooled specificity</td>
<td>0.92 (0.87-0.96)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>11.9 (6.8-20.8)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.10 (0.04-0.24)</td>
</tr>
</tbody>
</table>
### PCR IN BAL FLUID COMPARED WITH GM ASSAY


17 pts. with proven/probable IA

<table>
<thead>
<tr>
<th>Parameter for proven and probable IA vs no IA</th>
<th>MycAssay Aspergillus PCR</th>
<th>In-house Aspergillus PCR</th>
<th>GM ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Index cutoff, $\geq 1.0$</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>98.6 (94–99) [139/141]</td>
<td>97.9 (93–99) [138/141]</td>
<td>97.9 (93–99) [138/141]</td>
</tr>
<tr>
<td>Likelihood ratio $^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>67.2</td>
<td>42.0</td>
<td>44.8</td>
</tr>
<tr>
<td>Negative</td>
<td>0.06</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>88.9 (65–98) [16/18]</td>
<td>83.3 (58–96) [15/18]</td>
<td>84.2 (60–96) [16/19]</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>99.3 (96–99) [139/140]</td>
<td>98.6 (94–99) [138/140]</td>
<td>99.3 (96–99) [138/139]</td>
</tr>
<tr>
<td>DOR $^c$</td>
<td>1120.0</td>
<td>350.0</td>
<td>746.6</td>
</tr>
</tbody>
</table>

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$^a$ Of 158 patients studied, 17 were diagnosed with proven or probable IA according to the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria from 2002 (10).

$^b$ Likelihood ratio positive, sensitivity/1 – specificity; likelihood ratio negative, 1 – sensitivity/specificity.

$^c$ DOR, diagnostic odds ratio (likelihood ratio positive/likelihood ratio negative).
CLINICAL TRIALS

Experimental Treatment
May Be Right For You
GM-DRIVEN PRE-EMPTIVE THERAPY
MAERTENS J ET AL. CID 2005;41:1242
117 episodes of neutropenic fever.

In 41 episodes (35%) empirical AF criterion was satisfied (persistent or recurring fever), but only 9 (7.7%) in this group received AF.

Additional 10 episodes not clinically suspected of IA were detected and treated.

There were no undetected cases of IA. Only one case of zygomycosis was missed with this strategy.

12-week survival for patients with IA was 63.1%.
GM-GUIDED PRE-EMPTIVE VS EMPIRICAL STRATEGY: A RANDOMIZED STUDY

Preemptive arm
GM test twice a week

Empirical arm
No GM testing

Randomization

Single GM+
(≥0.5)

Urgent CT thorax

1) CT+
2) Rpt GM+

2
Start antifungals*

Repeat GM

27 pts

1) CT+
2) Rpt GM−

6
Start conventional AmB

1) CT−
2) Rpt GM−

1

GM−

If GM+

Continue twice-a-week GM

Febrile neutropenia protocol:
i.e., allow empirical antifungal therapy if indicated

10

25 pts

1) Positive histopathology or culture from any sterile site; or
2) Radiological studies suggestive of IFI

Start antifungal therapy only if:
GM-GUIDED PRE-EMPTIVE VS EMPIRICAL STRATEGY: A RANDOMIZED STUDY

<table>
<thead>
<tr>
<th></th>
<th>PRE-EMPTIVE* (n=27)</th>
<th>EMPirical (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at 12 weeks</td>
<td>85.2%</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Pre-emptive approach saved 11% of patients from antifungals.
Limited resources for GM monitoring?
PRE-EMPTIVE TREATMENT AFTER FEVER-DRIVEN DIAGNOSTIC WORKUP
Girmenia C. J Clin Oncol 2010;28:667

187 episodes

49 IFI

AF treatment

- 43% reduction in AF use
- 63% survival at 12 weeks
- 1.4 blood samples per episode for GM testing
POOR PERFORMANCE OF PCR

ORIGINAL ARTICLE

Randomized PCR-based therapy and risk factors for invasive fungal infection following reduced-intensity conditioning and hematopoietic SCT

O Blennow¹, M Remberger², L Klingspor³, B Omazic⁴, K Fransson⁴, P Ljungman⁵, J Mattsson⁴ and O Ringdén⁴

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Flawed randomization
Low incidence of IA in the first 100 days.
Lack of routine PCR testing after Day 100.
Better survival at day 30 (mortality 1.5% vs 6.3%), but no difference at day 100.
PRE-EMPTIVE VS. EMPIRICAL TREATMENT IN HIGH-RISK NEUTROPENIC PATIENTS

Prospective, randomized, open-label, non-inferiority

293 patients
Febrile at Day 4

EMPIRICAL
150

Pneumonia/sinusitis
Mucositis
Septic shock
Skin lesions
CNS symptoms
Splenic/hepatic abscess
Periorbital inflammation
Diarrhea
Aspergillus colonization
Positive GM (1.5)

PRE-EMPTIVE
143
### Pre-emptive vs. Empirical Treatment in High-Risk Neutropenic Patients


<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Empirical treatment arm (n = 150)</th>
<th>Preemptive treatment arm (n = 143)</th>
<th>Difference (95% CI)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive at study completion</td>
<td>146 (97.3)</td>
<td>136 (95.1)</td>
<td>-2.2 (-5.9 to 1.4)</td>
<td>.31</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFI</td>
<td>4 (2.7)</td>
<td>13 (9.1)</td>
<td>-6.4 (-10.9 to -1.9)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Baseline IFI due to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>2</td>
<td>6</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Candida species</td>
<td>0</td>
<td>3</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Breakthrough IFI due to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>2</td>
<td>2</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Candida species</td>
<td>0</td>
<td>2</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>IFI-related mortality</td>
<td>0 (0)</td>
<td>3 (2.1)</td>
<td>-2.1 (-4.1 to 0.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Duration of temperature ≥38°C, b days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>13 (5–21)</td>
<td>12 (5–20)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>1–42</td>
<td>1–59</td>
<td></td>
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</tbody>
</table>
PRE-EMPTIVE VS. EMPIRICAL TREATMENT IN HIGH-RISK NEUTROPENIC PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Emp (C/auto)</th>
<th>Pre (C/auto)</th>
<th>Emp (ind)</th>
<th>Pre (ind)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia, days</td>
<td>11</td>
<td>12</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Alive,%</td>
<td>100</td>
<td>97.1</td>
<td>94.9</td>
<td>93.2</td>
</tr>
<tr>
<td>IFI, n</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>AF Rx, %</td>
<td>38.9</td>
<td>18.6</td>
<td>82.1</td>
<td>58.9</td>
</tr>
<tr>
<td>Fever before Rx, days</td>
<td>6</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>LOS, days, mean</td>
<td>25.4</td>
<td>25.4</td>
<td>34.8</td>
<td>35</td>
</tr>
</tbody>
</table>

C: consolidation, auto: autologous-HSCT, ind: induction
CONCLUSIONS (CORDONNIER, 2009)

- Pre-emptive treatment was non-inferior to empirical approach for mortality at 2 weeks.
- The incidence of IFI was significantly higher in the pre-emptive group.
- No difference in nephrotoxicity.
- Antifungal use, days on antifungals, and the mean costs of antifungal drugs were significantly lower in the pre-emptive group.
- Empirical treatment may result in higher survival rates than would pre-emptive treatment in patients receiving induction chemotherapy.
March 2007-March 2009

397 patients

<table>
<thead>
<tr>
<th></th>
<th>Empirical</th>
<th>Pre-emptive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven/probable IFD</strong></td>
<td>14 (7.4%)</td>
<td>49 (23.7%)</td>
</tr>
<tr>
<td>n. (%)</td>
<td>7 molds</td>
<td>37 molds</td>
</tr>
<tr>
<td></td>
<td>7 yeasts</td>
<td>12 yeasts</td>
</tr>
<tr>
<td><strong>Death in patients with IFD</strong></td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>1 yeast¹</td>
<td>8 molds²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 yeasts³</td>
</tr>
<tr>
<td><strong>IFD-attributable mortality (%)</strong></td>
<td>1/14 (7.1)</td>
<td>11/49 (22.5)</td>
</tr>
<tr>
<td><strong>Overall 90-day mortality (%)</strong></td>
<td>12/190 (6.3)</td>
<td>33/207 (15.9)</td>
</tr>
</tbody>
</table>

*Older, more on salvage therapy than first-line, more on antifungal prophylaxis
Figure 1. Kaplan-Meier curves showing the impact of empirical (dotted line) versus pre-emptive (solid line) therapy on 90-day mortality in all 397 patients (A), and in the subgroup of 321 patients with AML at first line of treatment (B). $P=0.002$ for both A and B.
“Anyone for a game of Blind Man’s Bluff after dinner?”
SELECTION OF A STRATEGY

OPTIMAL DIAGNOSTIC FACILITIES
- Easy access CT facilities
- Well equipped laboratory

EXTENSIVE EXPERIENCE
- Specialists in house
- Common patient population

PRE-EMPTIVE APPROACH

LIMITED DIAGNOSTIC FACILITIES
LIMITED EXPERIENCE

EMPIRIC APPROACH

From: B. De Pauw
WHICH STRATEGY TO CHOOSE?

- **PROPHYLAXIS**
- **EMPIRICAL**
- **PRE-EMPTIVE**
- **TARGETED**

Availabilty of Dx tests

Incidence

IMMUNOSUPPRESSED

NON-IMMUNOSUP.

THANK YOU!