Why empirical antifungal strategy is outdated for fungal infections?

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How many patients do you treat according to the strategy you choose in high-risk neutropenic patients?

- Prophylaxis: 100%
- Empirical: 50-70%
- Pre-emptive GM: 15-40%
- Ttt: 5-10%

Estimated cost of treating a proven or probable invasive aspergillosis:
- 15,280 € (Slobbe 2008)
- to 442,233 $ (Tong 2009)
The main different antifungal approaches before overt fungal disease

- **Primary antifungal prophylaxis:** well defined, targeted to high-risk patients

- **Empirical antifungal therapy:** clinically defined, but poorly evidence-based

- **Pre-emptive antifungal therapy:** clinically defined and largely investigated
Historical Basis for Empirical Antifungal Treatment in Neutropenic Patients: the “fever-driven” approach

❖ Pizzo et al. 1982
  • 50 pts, febrile at day 7 of antibacterials
  • Trend for more IFI in the pts not receiving Ampho B

❖ EORTC 1989
  • 132 pts, febrile at day 4 of antibacterials. Ampho B at random
  • Less fungal deaths (6 vs 1; p = .056) with Ampho B

  • No impact on overall survival
“PRO” the Empirical Antifungal Approach

- Standard of care for persistent or recurrent fever
- Endorsed by consensus guidelines
- The early diagnosis of IFI is difficult
- Delayed treatment of IFI increases mortality
- Fever is easy to assess
- Sophisticated and expensive diagnostic exams can be spared or delayed
- The strategy is easy to apply
Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

« Generally recommended
Moderate evidence »
Why the empirical antifungal therapy is outdated?

- Many causes of non-infectious fever
- Probable overtreatment of many patients
- Excessive cost
- Unnecessary toxicity
- More efficient prophylaxis in well-defined populations
- Better imaging than 30 years ago
- Availability of new biomarkers (GM, PCR, β-D glucan, mannanes etc..)
- An approach of the previous century
“Taken as a measure against something possible, anticipated, or feared”

“Targeted”, “diagnosis-driven” ≠ fever-driven
OBJECTIVES
of a PRE-EMPTIVE strategy

Target only the high-risk patients

And at a very early phase of developing IFI

Reduce the administration of antifungals => reduce the costs

- less patients treated with ATF
- for shorter durations
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical:</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Imaging:</td>
<td>Typical or not</td>
</tr>
<tr>
<td>Biomarkers:</td>
<td>Galactomannan antigenemia</td>
</tr>
<tr>
<td></td>
<td>β-D glucan</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
</tr>
<tr>
<td></td>
<td>Mannan, antimannan</td>
</tr>
</tbody>
</table>

Combinations of several criteria
« PRE-EMPTIVE » for IFI
Should reproduce the successful CMV story?

<table>
<thead>
<tr>
<th>Pre-emptive in CMV Infection in HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV viremia is predictive for CMV disease</td>
</tr>
<tr>
<td><em>(Meyers 1990, Ljungman 1993)</em></td>
</tr>
<tr>
<td>Pre-emptive antiviral therapy based on detection of CMV Ag or nucleic acid is effective for prevention of CMV disease in allogeneic SCT patients</td>
</tr>
<tr>
<td>Pre-emptive treatment and prophylaxis are roughly equivalent</td>
</tr>
<tr>
<td><em>(Boeckh M et al. 1996)</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-emptive in IFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM Ag in blood as a predictor of IFI</td>
</tr>
<tr>
<td>Should prevent IF disease</td>
</tr>
<tr>
<td>Could replace prophylaxis for lower cost than empirical therapy</td>
</tr>
</tbody>
</table>
Galactomannan and CT-Based Preemptive Antifungal Therapy

Maertens et al. Clin Infect Dis 2005

High-risk hematology patients

Daily GM monitoring and clinical evaluation

OD index
2x ≥ 0.5

5 Days of unexplained Neutropenic fever Refractory to Antibiotics or relapsing

New infiltrate on chest X-Ray or signs/symptoms Of invasive mycosis

Positive culture or Microscopy (molds)

Thoracic CT scan (± CT sinus)

Characteristics of invasive Mycosis: ‘halo-sign’

Atypical lesion

Normal

Thoracic CT & BAL

Bronchoscopy with BAL

Broad-spectrum antifungal therapy

Continued monitoring No antifungal therapy
Galactomannan and CT-Based Preemptive Antifungal Therapy

Maertens et al. CID 2005

136 episodes

117 febrile episodes

41 episodes = 30% with criteria for Empirical therapy

9 episodes treated in the Pre-emptive approach + 10 with GM+ (febrile or not)

TOTAL: 16% of the whole episodes received antifungals

Incidence of probable and proven IFI / episode: 15%

/ patient: 24%
Liposomal Amphotericin B Tx. Following Allogeneic SCT PCR-based vs. Empiric Antifungal Therapy

Allogeneic myeloablative SCT recipients followed from D0 to D100

Conditioning Therapy

PCR-based

PCR pos. ± clinical signs

PCR neg. + febrile neutropenia ≥ 120h

Randomization

Empirical Therapy

Febrile neutropenia ≥ 120h

Liposomal Amphotericin B 3 mg/kg/d for 3 days

Clinically stable

Liposomal Amphotericin B 1 mg/kg/d

Clinically deteriorated

Liposomal Amphotericin B 3 mg/kg/d

Endpoints: Incidence of IFI, IFI-related Mortality, Overall Survival

Hebart H et al. BMT 2009
PCR-based Pre-emptive Approach in Allogeneic SCT

Hebart H et al. BMT 2009

403 Allogeneic SCT pts until D100 At random

PCR screening
n=196

Treated: 109 (56%)*

Proven IFI: 11**

Death before d30: 4***

* p<0.05

** ns

Empirical Antifungal therapy
n=207

Treated: 76 (37%)*

Proven IFI: 16 **

Death before d30: 13***

*** p=.03
A randomized comparison between empirical vs. pre-emptive antifungal strategy in high-risk neutropenic patients
The “Prevert” study

Randomization at start of chemo
day 2 of fever under ATB at the latest
GM screening x 2 /week
Daily clinical evaluation

Empirical
Fever driven

Pre-emptive
Only if pneumonia, shock, skin lesions evocative of IFI, sinusitis, orbititis, HS abscesses, grade 4 mucositis, Asp colonization, Or one GM Ag +

In both groups: Ampho B (1mg/kg/d) or liposomal Ampho B (3mg/kg/d) according to the daily assessment of the creatinin clearance

Cordonnier et al. CID 2009
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Empiric Group (N=150)</th>
<th>Preemptive Group (N=143)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Mean (SD)</td>
<td>52.0 (13.5)</td>
<td>52.1 (14.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Primary Diagnosis, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>66.0</td>
<td>68.5</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>5.3</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Lymphoma / myeloma</td>
<td>26 / 2.7</td>
<td>25.2 / 4.2</td>
<td></td>
</tr>
<tr>
<td>Hematological treatment, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction / relapse treatment</td>
<td>46.7 / 5.3</td>
<td>46.8 / 4.2</td>
<td></td>
</tr>
<tr>
<td>Consolidation</td>
<td>18.0</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Autologous SCT (with TBI)</td>
<td>30.0 (17.8)</td>
<td>32.2 (13)</td>
<td></td>
</tr>
<tr>
<td>Mean duration of PMN&lt;0.5 (sd)</td>
<td>20.3 (10.4)</td>
<td>20.0 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Azole prophylaxis Fluco / Itra</td>
<td>11.3 / 6.7</td>
<td>13.3 / 4.2</td>
<td>NS</td>
</tr>
</tbody>
</table>
Empirical v. Preemptive antifungal therapy in high risk neutropenic patients (n = 293)

Overall survival

Primary endpoint

Proven and probable IFI

Cordonnier et al. CID 2009
# Study 65091 EORTC

<table>
<thead>
<tr>
<th>Title</th>
<th>Empirical versus “pre-emptive” antifungal therapy of patients with haematological malignancies and recipients of an allogeneic HSCT following myeloablative therapy. A therapeutic phase III strategy study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>MSD</td>
</tr>
</tbody>
</table>

- Includes allogeneic myelo-ablative transplant
- Excludes autologous SCT and consolidation phases of AL
- Prophylaxis by Fluconazole for all the patients
- Cut-off of GM Ag to start the antifungal in the pre-emptive trial: 1 serum or plasma test > 0.5 l
## Other studies on the pre-emptive approach in neutropenic patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No. Pts or episodes</th>
<th>Allo HSCT</th>
<th>Design / indication for antifungals</th>
<th>% IFI</th>
<th>Antifungal agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girmenia</td>
<td>Observational</td>
<td>220 ep.</td>
<td>0</td>
<td>Intensive diagnosis work-up if fever &gt; 4d or recurrent fever (3 consecutive daily GM, chest CT)</td>
<td>24%</td>
<td>5 different drugs</td>
</tr>
<tr>
<td><em>JCO 2009</em></td>
<td>Single center</td>
<td>In 146 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnes</td>
<td>«</td>
<td>125 pts</td>
<td>18%</td>
<td>GM and PCR x2/w</td>
<td>33.6%</td>
<td>Caspo / L-AmB/Vori</td>
</tr>
<tr>
<td><em>JCP 2009</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aguilar-Guisado</td>
<td>«</td>
<td>347 ep. in 66 pts</td>
<td>13.6%</td>
<td>Clinically driven (sepsis/shock, lung, CNS, sinus, abdominal, skin)</td>
<td>4.5%</td>
<td>4 different drugs</td>
</tr>
<tr>
<td><em>BMT 2009</em></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dignan</td>
<td>Retrospective</td>
<td>99 pts</td>
<td>All, 63 RIC</td>
<td>Chest CT at 72h of fever, then every 10-14 days</td>
<td>4%</td>
<td>Caspo → L-AmB or Vori</td>
</tr>
<tr>
<td><em>BMT 2009</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pagano</td>
<td>Observational</td>
<td>397 pts</td>
<td>+</td>
<td>GM and CT-scan</td>
<td>23.7%</td>
<td>5 different drugs or combination</td>
</tr>
<tr>
<td><em>Haematologica 2011</em></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluation on practice of empirical versus pre-emptive therapy: the HEMA @-Chart project  
Pagano et al. 2011

Observational study in 23 italian centers, 2007-2009
397 Pts, AL, 1st induction mainly, autologous and allogeneic SCT
Under antiF prophylaxis: 48% in E, 58% in PE
« Almost identical diagnostic work-up », multiple ATF, possible bias

<table>
<thead>
<tr>
<th></th>
<th>Empiric N=190</th>
<th>Preemptive N=207</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven+probable IFD</td>
<td>7.4%</td>
<td>23.7%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mould infections</td>
<td>7</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Overall d90 mortality</td>
<td>6.3%</td>
<td>15.9%</td>
<td>.002</td>
</tr>
</tbody>
</table>
Finally, PNEUMONIA, much more than GM+, is often the main criteria to start ATFs in pre-emptive studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. PE Pts or episodes/No. Total Pts</th>
<th>Criteria fixed by study design</th>
<th>Criteria to start ATF among pts who received ATFs</th>
</tr>
</thead>
</table>
| Cordonnier 2009   | 143 / 293                            | GM or clinical criteria        | Pneumonia 46.4%  
|                   |                                      |                                | Severe mucositis 17.9%  
|                   |                                      |                                | GM +-alone 5.4%       |
| Aguilar-Guisado 2009 | 347                                 | Clinical criteria only         | Shock 34.6%  
|                   |                                      |                                | Pneumonia 19%  
|                   |                                      |                                | Other focus 11.5% |
| Pagano 2011       | 207 / 397                            | # GM or CT Scan or multisite colonization | CT-scan + GM+ 78%  
|                   |                                      |                                |                        16% |
Pre-emptive approach in practice: When to do a CT-scan

- A new cough, chest pain or hemoptysis
- An abnormal chest radiograph
- A positive culture for *Aspergillus* or other mold from any site
- Microscopic evidence of hyphae in any invasive sample
- Unresolved temperature after 7 days of antibiotics and/or antifungals

*Guidelines from the British Society for Medical Mycology- Denning et al. Lancet Infect Dis 2003; 3: 230*

And of course, in case of *Positive Galactomannan/ β-D-glucan/PCR assay(s)*
Pre-emptive antifungal therapy …

….. alternative to prophylaxis …

… should costs be the main driver..

… moving towards a more rational, tailored approach to the management of IA
CONCLUSION: Do not give empirical antifungals anymore

The pre-emptive approach with GM and CT-scan:

- is elegant
- is a logical approach as far as IA Is the main concern
- reduces the use of antifungals
- reduces antifungal costs and saves money for the lab

New markers to be explored for unclassical IFI