Pre-emptive Antifungal Treatment in High Risk Patients

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Infectious Causes of Persistent Fever in Neutropenic Patients

- Resistant bacteria or slow response
  - Abscess
  - Prosthetic material

- Non-bacterial infection
  - Fungi
  - Viruses
  - Parasites
Non-infectious Causes of Fever in Neutropenic Patients

- Cytokines
- (Auto)immune reactions
- Blood products
- Toxins
- Medicine
- Tissue (tumor) products
Drawbacks of Empirical Treatment

- Overtreatment
- Breakthrough fungal infections
- Drug interactions
- Adverse effects
- Emergence of resistance
- Cost
MULTIDISCIPLINARY WORK

Clinician

Microbiologist

Pathologist

Infectious Disease Physician

Pharmaceutical Industry

From Peter Donnelly
Pre-emptive=Diagnostic-Driven= Deferred Systemic Antifungal Treatment

Treatment that is delayed until there is substantial evidence for the presence of an invasive fungal infection
SIGNS & SYMPTOMS IN IA

Cornillet A, et al. CID 2006;43:577
Imaging Clues
The CT halo sign is described as a mass-like infiltrate with a surrounding halo of ground glass attenuation. The halo lesion was shown to correspond to a central fungal nodule surrounded by a rim of hemorrhage and coagulative necrosis. This halo sign is highly indicative of IPA and, it occurs early in the course of IPA, during the neutropenic period.
The air-crescent sign is a pulmonary cavitation. It is a later sign that appears with the bone marrow recovery. This air-crescent sign is not pathognomonic of aspergillosis, but in the setting of leukemic patients, it is highly suggestive.

Evolution of CT scan images in invasive pulmonary aspergillosis

- **Halo sign**
  - D 0 - 5

- **Air-space consolidation**
  - D 5 - 10

- **Air-crescent sign**
  - D 10 - 20

**Neutropenia**

Caillot et al 2001
Days to Dx after the 1st suspicion is 2 1 days if systematic CT compared to 7 5 days when taken only indicated.

How frequently?
### Table 4. Investigations in both the empirical and the diagnostic-driven pathway

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Timelines and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic investigations</strong></td>
<td></td>
</tr>
</tbody>
</table>
| chest CT (preferably volume acquisition with thin slice reconstruction) | initial persistent fever  
repeat frequency no sooner than 2 weeks, unless significant clinical deterioration |
| CT/MRI other sites biopsy respiratory secretions   | according to clinical features  
every attempt should be made to obtain tissue (allows proven diagnosis to be made)  
bronchoalveolar lavage should be undertaken following the earliest radiological evidence when  
a patient is unresponsive to antibiotics  
during fever; if positive for fungus repeat daily until negative  
this can be performed to provide support for the diagnosis of invasive aspergillosis  
several samples should be sent on consecutive days |
| serum/plasma galactomannan                          | pre-therapy and throughout the risk period  
twice weekly during admission  
can help exclude aspergillosis because of the high negative predictive value  
detection of galactomannan has been used as a criterion for starting therapy  
pre-therapy and throughout the risk period  
twice weekly during admission  
data suggest that some PCR tests can help exclude aspergillosis and candidosis because of the  
high negative predictive value  
detection of fungal nucleic acid might be useful as a criterion for starting therapy  
efforts are under way to define a standard for *Aspergillus* PCR  
pre-therapy and throughout the risk period  
twice weekly during admission  
might help exclude aspergillosis and candidosis because of the high negative predictive value  
detection of β-d-glucan might be useful as a criterion for starting therapy |
| whole-blood PCR                                     |                                                                                        |
| serum β-d-glucan                                    |                                                                                        |
THE STORY OF AN AML PATIENT

Central venous catheter
mucositis

PNL
THE STORY OF AN AML PATIENT

25 yo male
AML

Central venous catheter

Biomarker

mucositis

PNL

°C

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Serum GM as a Surrogate Marker: Autopsy Study


Sens. 92.6%
Spec. 95%
PPV 93%
NPV 95.4%
TIMING IN ALLO-HSCT

Maertens et al. JID 2002;186:1297.
Biomarkers as Diagnostic Tests

- **Galactomannan ELISA assay**
  - GM is a cell wall constituent released during hyphal growth in tissue
  - Can be detected early
  - Sens 0.78, Spe 0.81/ PPV 0.3 to 0.6, NPV 0.95 (very heterogenous)
  - Twice weekly screening is recommended
  - 0.5 OD positive

- **PCR**
  - Test characteristics vary enormously from study to study
  - Not standardised and clinically validated

- **β-d-glucan**
  - Present in the cell wall of most fungi incl Candida, Aspergillus, Fusarium...
  - Meta-analysis: Sens 0.5, Spe 0.99/ PPV 0.84, NPV 0.95
GM-guided vs. Empirical Strategy: A Randomized Study

Empirical vs Preemptive Treatment: RCT

- Non-inferiority study (NI margin -8%)
- All patients were monitored with serum GM twice weekly (positive value: $\geq 1.5$).
- Results were available within 24 h.

<table>
<thead>
<tr>
<th>293 patients</th>
<th>Still febrile at Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>empirical</td>
<td>150</td>
</tr>
<tr>
<td>Pre-emptive</td>
<td>143</td>
</tr>
</tbody>
</table>

AmB-deoxycholate

Consistent w/ non-inferiority of preemptive

<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>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Alive at study completion</em></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><em>IFI</em></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><em>Aspergillus species</em></td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida species</em></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><em>Aspergillus species</em></td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida species</em></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>
<td></td>
</tr>
</tbody>
</table>

Non-inferiority margin was chosen as -8 as the lowest value for CI.

**Subgroup Analysis**

GM cut-off was >1.5
Treatment start on 6th day in empirical arm vs 13th in preemptive arm

### SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>EMPIRICAL</th>
<th>PRE-EMPTIVE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>94.9%</td>
<td>93.2%</td>
<td>*-8.0 to 4.6</td>
</tr>
<tr>
<td>Consolidation</td>
<td>100%</td>
<td>97.1%</td>
<td>-6.1 to 0.4</td>
</tr>
</tbody>
</table>

*Inferiority can not be ruled out.

Of 17 IFD cases, 15 occurred in the induction Rx group, and 2 in the consolidation therapy subgroup (16.4% vs. 3.9%, p<.01).

_Cordonnier C, et al. CID 2009;48:1042._
Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial

C Orla Morrissey, Sharon C-A Chen, Tania C Sonell, Samuel Milliken, Peter G Bardy, Kenneth F Bradstock, Jeffrey Sarr, Catriona L Halliday, Nicole M Gilroy, John Moore, Anthony P Schwarzer, Stephen Guy, Ashish Bajel, Adrian R Tramontana, Timothy Spelman, Monica A Slavin, for the Australasian Leukaemia Lymphoma Group and the Australia and New Zealand Mycology Interest Group

*Lancet Infect Dis 2013; 13: 519-28*
<table>
<thead>
<tr>
<th></th>
<th>Standard diagnosis group (n=122)</th>
<th>Biomarker diagnosis group (n=118)</th>
<th>% difference between groups (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received empirical treatment with antifungal drugs</td>
<td>39 (32%)</td>
<td>18 (15%)</td>
<td>17% (14 to 26)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>18 (15%)</td>
<td>12 (10%)</td>
<td>5% (-4 to 14)</td>
<td>0.31</td>
</tr>
<tr>
<td>Invasive aspergillosis-related</td>
<td>6 (5%)</td>
<td>3 (3%)</td>
<td>2% (-2.5 to 7.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Other invasive fungal disease-related*</td>
<td>0</td>
<td>2 (2%)</td>
<td>...</td>
<td>0.24</td>
</tr>
<tr>
<td>Incidence of invasive aspergillosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>...</td>
<td>1.0</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>16 (14%)</td>
<td>-14% (-20 to -7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Possible</td>
<td>0</td>
<td>6 (5%)</td>
<td>-5% (-9 to -1)</td>
<td>0.013</td>
</tr>
<tr>
<td>Incidence of other invasive fungal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven</td>
<td>4 (3%)</td>
<td>5 (4%)</td>
<td>...</td>
<td>0.75</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>1 (1%)</td>
<td>...</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Data are n (%). Results for possible other invasive fungal disease are not shown because cases were not individually identified by microscopic or culture methods. *Scedosporium prolificans fungaemia (n=1), disseminated mucormycosis (Rhizopus sp; n=1). †Candida guilliermondii (n=1), Candida glabrata (n=3), Candida krusei (n=1), Candida parapsilosis (n=1), Rhizopus sp (n=1), Rhizopus microsporus (n=1), S prolificans (n=1), Exserohilum sp (n=1).

Table 2: Empirical treatment with antifungal drugs, mortality, and incidence of invasive fungal infections through 26 weeks of follow-up
Summary

- Clinical management of high risk patients can be guided by GM and PCR in combination
- Empirical use reduced 52%
- No cases of IA were missed by the biomarker group
- Biomarker-based strategy can be used in routine clinical practice to differentiate patients with and without IA
Patients at high risk of invasive fungal disease

Reserve empirical treatment with antifungal drugs for patients with persistent febrile neutropenia in whom an invasive fungal disease is suspected or patient is unwell:
- When diagnostic tests are unavailable*
- For a short time until diagnosis of invasive fungal disease is confirmed or excluded

Not on prophylaxis
- Biomarker-based diagnostic strategy

On fluconazole or itraconazole prophylaxis
- Biomarker-based diagnostic strategy

On voriconazole or posaconazole prophylaxis
- Targeted diagnostic strategy
  - Bronchoscopy
  - High-resolution CT-guided fine needle aspirate
  - Biopsy

*The diagnostic tests available are not detailed in this diagram.
Limited resources (human, money) for biomarker or radiological monitoring?
# Pros vs Cons

<table>
<thead>
<tr>
<th>Pros vs Cons</th>
<th>Diagnostic-driven</th>
<th>Empirical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>Center-dependent</td>
<td>+++</td>
</tr>
<tr>
<td>Safety</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
<td>Antifungal: ↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Diagnostic tests: ?</td>
<td></td>
<td>?</td>
</tr>
</tbody>
</table>
Laboratory tempo

Opening hours
Mon - Fri 09:00 - 17:00
Sat 09:00 - 12:00
CLOSED on Sundays & Public Holidays

Meeting in Progress
Is GM/BDG -effective as a screening test?

- Good technical infrastructure of the lab.
- Standardized flowcharts for sampling and testing
- Reporting in 24 hours
WHICH STRATEGY?

OPTIMAL DIAGNOSTIC FACILITIES
- Easy access to CT and its report.
- Well-equipped lab.

EXTENSIVE EXPERIENCE
- Presence of experts
- A broad spectrum of patients

LIMITED DIAGNOSTIC FACILITIES
LIMITED EXPERIENCE

PRE-EMPTIVE APPROACH

EMPIRICAL APPROACH

Courtesy of Ben dePauw