TREATMENT STRATEGIES FOR INVASIVE FUNGAL INFECTIONS

Part I: EMPIRICAL THERAPY
CAUSES OF DEATH IN PATIENTS WITH MALIGNANCIES
NIJMEGEN, THE NETHERLANDS

n = 328

BACTERIAL INFECTION 7%
FUNGAL INFECTION 36%
MULTIFACTORIAL 40%
HEMORRHAGE 17%
22% non-relapse mortality

n = 163

9% mould-related deaths

39% mould-related
PROPHYLAXIS          EMPIRICAL THERAPY          THERAPY

invasive fungal infection
NOT PRESENT

invasive fungal infection
NOT EXCLUDED

invasive fungal infection
invasive fungal infection
NOT EXCLUDED
MORTALITY OF INVASIVE ASPERGILLOSIS

Variation due to:

- timing of intervention
  (timely diagnosis)
EVOLUTION OF AN INFECTION AND MORTALITY

FUNGAL BURDEN

22%

97%
134 cases of candidemia

- within 12 hrs: 0%
- 12-24 hrs: 5%
- 24-48 hrs: 10%
- >48 hrs: 15%

mortality
ITRACONAZOLE VS AMPHOTERICIN-B FOR FUNGAL INFECTIONS IN NEUTROPENIA

UNIVERSITY HOSPITAL NIJMEGEN

n = 64

<table>
<thead>
<tr>
<th>DOCUMENTED</th>
<th>ITRACONAZOLE</th>
<th>AMPHOTERICIN-B</th>
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</thead>
<tbody>
<tr>
<td>RESPONSE RATES</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>PROBABLE</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>POSSIBLE</td>
<td>80%</td>
<td>65%</td>
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SURVIVAL OF ASPERGILLOSIS IN RELATION TO PRESUMED RISK FACTORS


n = 289
IMPACT OF EARLY VERSUS LATE INTERVENTION

Clinical symptoms not characteristic

Manifestations on imaging seldom specific

Biopsy often precluded by co-morbidity
Review of 391 cases of IFI in patients with hematological malignancies:

- Not diagnosed ante mortem 21%
- BAL culture sensitivity 66%
Review of 97 autopsies after allogeneic bone marrow transplantation:

- Invasive fungus NOT diagnosed ante mortem:

  60% (in spite of galactomannan screening)
UP TO 30% OF PATIENTS WITH INVASIVE FUNGAL DISEASE AT AUTOPSY NEVER RECEIVED ANY SYSTEMIC ANTIFUNGAL THERAPY
YIELD OF DIAGNOSTIC PROCEDURES AND EVOLUTION OF FUNGAL INFECTION

time

evolution of the infection

yield of diagnostic interventions
MAKE YOUR CHOICE!

[Sequence of images showing a character carrying a large object, possibly a balloon, with a question mark in the background. The character appears to be running or moving.]
AMPHOTERICIN-B FOR FEVER PERSISTING 4-7 DAYS

PERCENTAGE OF SYSTEMIC FUNGUS

Pizzo et al AJM 1982  
16 vs 18 pat

EORTC AJM 1989  
64 vs 68 pat

NO AMPHO-B  31%  9%

AMPHO-B  6%  2%
THE BASIS FOR EMPIRIC ANTIFUNGAL THERAPY IN FEBRILE NEUTROPENICS


Persisting FUO and neutropenia (n=50)

- Stop all antibiotics n=16
- Continue n=16
- Add 0.5 mg/kg/day amphotericin n=18

-6%
-36%
-6%

Fungal infections
EARLY EMPIRICAL ANTIFUNGAL THERAPY IN FEBRILE NEUTROPENICS


- Continue antibiotics (n=64)
  - 50%

- Persisting FUO or CDI and neutropenia

- Add 0.6 mg/kg/day amphotericin (n=68)
  - 69%

- DEFERVESCENCE
  - With prophylaxis (61): 61
  - No prophylaxis (45): 78
  - CDI (41): 75
ADMINISTRATION OF ANTIMICROBIALS IN RELATION TO THE COURSE OF NEUTROPENIA

antibacterials

Empirical antifungals
Still fever despite antibiotics
... it can be a fungus!
SYMPTOMS OF INVASIVE ASPERGILLOSIS IN NEUTROPENIA AND NON-NEUTROPENIA

88 cases

- Fever
- Dyspnea
- Cough
- Chest pain
- Neurology
- Skin
- Hemoptysis
- Bacterial
- Halo sign

Total: 100
Neutropenia: 90
Non-neutropenia: 100
... it can be a fungus!
..so, what can I do?
... it can be a fungus!

Diagnosis

Change antibiotics
GROWTH OF ASPERGILLUS

1-2 cm per 24 hours
ONE WEEK LATER....
Diagnosis

Change antibiotics

Course of
Peter Donnelly
Empirical antifungal therapy

Diagnosis

Change antibiotics
REPORTED NEED FOR EMPIRICAL ANTIFUNGALS

- Cordonnier (2006 Blood)
- Behre (1995 Ann Hema)
- Nucci (2000 CID)
- Harrouseau (2000 AAC)
- Penack (2005 ICAAC)
- Mattiuzi (2003 Cancer)
- Winston (1993 Annals)
- Rotstein (1999 CID)
- Slavin (1995 JID)
- Goodman (1992 NEJM)
UNEXPLAINED FEVER AND NEUTROPENIA

antibiotics for 3-5 days

DEFERVESCENCE

NO DEFERVESCENCE

ANTIFUNGAL
Do You Use Empirical Antifungal Therapy?

- YES: 97%
- NO: 3%

n=38

Time of initiation?
First febrile episode 5 d (3 to 8.5) vs. Fever relapse 3 d (1 to 8.5) p<0.001

PERCEIVED NEED OF EMPIRICAL THERAPY

(EUROPEAN GUIDELINE EXPERTS)

E.C.I.L.
THE DUEL

DIAGNOSIS vs. THERAPY
NEW DIAGNOSTIC TOOLS?

HIGH RESOLUTION CT SCAN

GALACTOMANNAN

β-D-GLUCAN

PCR

22%

FUNGAL BURDEN

NEW TOOLS

TRADITIONAL DIAGNOSIS
IMPACT OF SYSTEMATIC CT-SCAN ON THE OUTCOME OF PULMONARY ASPERGILLOSIS


RETROSPECTIVE ANALYSIS
n = 37

SYSTEMATIC CT-SCAN
BEFORE      AFTER

DAYS TO DIAGNOSIS
FROM FIRST MOMENT OF SUSPICION 7 ± 5 2 ± 1
LEVEL OF GALACTMANNAN TITER: INDICATIVE OF FUNGAL MASS  
*Marr et al. J Infect Dis 2004;190:641-649*

1106 samples from 79 bone marrow transplant recipients

<table>
<thead>
<tr>
<th>Overall</th>
<th>number</th>
<th>positive test</th>
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<tbody>
<tr>
<td>Proven</td>
<td>8</td>
<td>62%</td>
</tr>
<tr>
<td>Probable</td>
<td>5</td>
<td>40%</td>
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LEVEL OF GALACTOMANNAN TITER: INDICATIVE OF FUNGAL MASS

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<table>
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<tr>
<th>On antifungals</th>
<th>number</th>
<th>positive test</th>
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<tbody>
<tr>
<td>Proven</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td>Probable</td>
<td>5</td>
<td>17%</td>
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<table>
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<th>No antifungals</th>
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<tr>
<td>Proven</td>
<td>7</td>
<td>88%</td>
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149 episodes in 96 patients with hematological malignancy

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<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>P.P.V.</th>
<th>N.P.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactomannan ELISA</td>
<td>100%</td>
<td>55%</td>
<td>100%</td>
</tr>
<tr>
<td>(cut-off 0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>55%</td>
<td>40%</td>
<td>96%</td>
</tr>
<tr>
<td>Glucan-test</td>
<td>55%</td>
<td>40%</td>
<td>96%</td>
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201 febrile episodes in patients with hematological malignancy

2x weekly PCR-ELISA and Galactomannan

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<th>Sensitivity</th>
<th>Specificity</th>
<th>P.P.V.</th>
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<tbody>
<tr>
<td>Galactomannan (cut-off 0.5)</td>
<td>75%</td>
<td>22%</td>
<td>9%</td>
</tr>
<tr>
<td>PCR</td>
<td>88%</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>PCR + galactomannan</td>
<td>100%</td>
<td>11%</td>
<td>10%</td>
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"I’m stumped. We’ll have to wait for the autopsy."
FIRST TEST POSITIVE FOR ASPERGILLOSIS IN HEMATOLOGICAL MALIGNANCIES


55 patients

0 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

DAYS

GM antigen

PCR

CT

culture histology

55 patients
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

EMPIRICAL APPROACH
OUTCOME OF SEROLOGIC TESTS AND IMPLICATIONS FOR TREATMENT OF INVASIVE FUNGAL INFECTIONS

*POSITIVE
does not prove infection

PAY ATTENTION
ALWAYS BE CAREFUL !!!!

*NEGATIVE
does not exclude infection
EMPIRICAL OR PRE-EMPTIVE?

PRE-EMPTIVE
imaging
clinics
laboratory

143
9%
€2218
95%

293
neutropenic patients

End of neutropenia
invasive fungus

antifungals
mean costs
survivors

3% 66% €2337
98%

EMPIRIC
3 days
persisting fever

150
TREATMENT STRATEGIES OF ASPERGILLOSIS ARISING DURING AML IN DAILY PRACTICE

Pagano et al. SEIFEM 2008

140 probable/proven cases

- Empirical: 62%
- Pre-emptive: 29%
- Targeted: 9%

Attributable mortality 27%
BUILDING AN ANTIFUNGAL STRATEGY

EMPIRICAL ADMINISTRATION ANTIFUNGALS

therapeutic
antifungals
diagnostics

prophylaxis
prevention
VORICONAZOLE FOR ASPERGILLOSIS AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION


[Graph showing the probability of death over time for different years post-transplantation]
A little bit of fluco makes me smile
A little bit of ampho for my pride
A little bit of lipo for a while
A little bit of Cancidas by my side
Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II