Strategies in antifungal therapy: the neutropenic patient

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University of Genova, Genova, Italy
THERAPEUTIC STRATEGIES

Treatment

Prophylaxis
Empiric
Presumptive or preemptive
Specific

Disease likelihood

Remote
Possible
Probable disease
Proven

Temperature

Granulocytes

Days of neutropenia

Culture
Tissue
Galactomannan
Empiric antifungal therapy

To administer an antifungal after a course (nobody knows how long) of antibacterial therapy in persistently febrile and neutropenic patients despite broad-spectrum antibacterial therapy.
**Rationale for empirical therapy**

- Delaying therapy until diagnosis is established may lead to dissemination
- Persistent fever and neutropenia day 4-7 is one of the predictors of IFI
- Empirical antifungal therapy can suppress fungal overgrowth secondary to antibacterial therapy
- Individual experience (anecdotical) of dramatic cases of neutropenic patients with persistent FUO, who were demonstrated at autopsy to have disseminated fungal infections
- No diagnostic tools in the seventeens
  - Chest-x-rays often at bedside of no utility
  - Biopsy impossible
  - BAL and culture poorly sensitive and sometimes harmful
Historical clinical trials of empiric antifungal therapy

- P. Pizzo et al.  

- EORTC-IATCG (F. Meunier et al)  
Empiric antifungal therapy unblinded, randomized clinical trial

Study design

- 50 patients not responding to empiric antibacterial therapy
- persistent neutropenia

Continue antibacterial therapy (16 pts.)
- 1 bact. infection
- 6 fungal infections

Discontinue antibacterial therapy (16 pts.)
- 5 bact. infection
- 2 fungal infections

Continue antibacterial and add Am B (18 pts.)
- no bact. infection
- 1 fungal infection
- 1 viral infection (CMV)

Meunier F. et al. on behalf of the EORTC-International Antimicrobial Therapy Cooperative Group

Empirical antifungal therapy in febrile, granulocytopenia patients

Study design
unblinded, randomized clinical trial

Fever

Empirical antibacterial therapy

Day 5-7
- no documentation
- persistent granulocytopenia and fever

Am B

No antifungal therapy

EORTC-IATCG Am J Med 1989
Empiric antifungal therapy: mortality and cause of death

<table>
<thead>
<tr>
<th></th>
<th>AmB</th>
<th>Nil</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (day 30)</strong></td>
<td>11/68 (16%)</td>
<td>14/64 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal infection</td>
<td>0/68 (0%)</td>
<td>4/64 (6%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>1/68 (1%)</td>
<td>2/64 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>10/68 (15%)</td>
<td>8/64 (12%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

EORTC - IATCG Am J Med 1989
The EORTC study suggests that empiric AmB might be indicated in febrile and neutropenic cancer patients not responding to initial antibacterial therapy with no microbiological documentation of infection. In particular, adult patients not receiving antifungal prophylaxis were most likely to benefit from this approach.
Nevertheless

- Regulatory agencies give approval for the indication
- The IDSA endorsed empirical antifungal therapy in its guidelines for febrile neutropenia, although with some limitation
IDSA 2002 guidelines for febrile neutropenia

Persistent fever during first 3-5 days of treatment: no etiology

Reassess patient on days 3-5

- Continue initial antibiotics
- If no change in patient's condition (consider stopping vancomycin)

- Change antibiotics
- If progressive disease, -if criteria for vancomycin are met

- Antifungal drug, with or without antibiotic change
- If febrile through days 5-7 and resolution of neutropenia is not imminent

Guide to treatment of patients who have persistent fever after 3-5 days of treatment and for whom the cause of the fever is not found.
““In two randomized, placebo controlled trials, the frequency of proved invasive fungal infections was reduced in patients treated empirically with conventional amphotericin B deoxycholate””

TJ Walsh et al.
N Engl J Med 1999
Empirical antifungal therapy

**Pro**
- mild effects in 2 randomized, open-label studies in preventing fungal infections and fungal deaths
- some indication that empirical AmB might have a positive effect on the death rate (The Cochrane Library)
- Emotion-driven

**Cons**
- Overtreatment, which forgets that pts. with IFI may have little or no fever
- Potentially toxic
- Very expensive
- Diagnosis not done
- Too much therapy if no infection, but not enough therapy, if there is an IFI
EMPIRICAL ANTIFUNGAL THERAPY OF NEUTROPENIC PATIENTS WITH PROLONGED FEVER DESPITE ANTIBACTERIAL THERAPY

<table>
<thead>
<tr>
<th>Empirical therapy</th>
<th>ECIL 2009</th>
<th>IDSA 2008</th>
<th>BSH 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-AMB</td>
<td>B II</td>
<td>A I</td>
<td>A I</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>A I</td>
<td>A I</td>
<td>If given, A I</td>
</tr>
<tr>
<td>ABLC / ABCD</td>
<td>B I</td>
<td>A I</td>
<td>-</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>B I</td>
<td>A I</td>
<td>-</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>B I</td>
<td>A I</td>
<td>-</td>
</tr>
<tr>
<td>D-AMB</td>
<td>B / D I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>C I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micafungin</td>
<td>B II</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L-AMB or Caspofungin in children</td>
<td>B II</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
• **Empirical** use of systemic antifungal agents as treatment of fever of unknown origin (FUO) which is “resistant” to broad spectrum antibacterial therapy should be **discouraged**.

• When antifungal therapy is unavoidable because of possible IFI, justification for this use should be sought from **CT scans and mycological tests**.

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**2008 BSH Guidelines – key recommendations**
BSH: Shift versus **pre-emptive**, and not empirical antifungal therapy.

- The need for systemic antifungal therapy should be confirmed by CT scans and mycological testing for fungal wall components (GM and/or BG) in blood or BAL.
- If these are non-confirmatory, empirical therapy may be unnecessary and could be avoided or stopped. It is unclear whether PCR detection of fungal DNA is as reliable as fungal antigen tests (grade B, level IIa)
Rationale for pre-emptive treatment

- Too many patients receive empirical AF therapy unnecessarily
- Targeting the high risk patient (AML, allo HSCT) is a logical response
- Using an individualized approach seems even more logical
- There are new diagnostic advances
  - Galactomannan monitoring
  - Early and repeated lung CT scan
  - Maybe beta-D-glucan
  - PCR in the future?
ABLC VS AMB AS ANTIFUNGAL THERAPY IN GRANULOCYTOPENIC CANCER PATIENTS WITH UNEXPLAINED FEVER NOT RESPONDING TO EMPIRICAL ANTIBACTERIAL THERAPY.
(by C. Viscoli, D. Denning, B. de Pauw)

2. OBJECTIVES

1. To compare safety and efficacy of ABLC and AmB in granulocytopenic cancer patients with unexplained fever.
2. To compare the relative merits of early empirical antifungal therapy (from now on denominated “early empiric therapy”) versus clinically, instrumentally and/or microbiologically-oriented antifungal therapy (from now on denominated “watchful waiting”) in granulocytopenic cancer patients with unexplained fever not responding to empirical antibacterial therapy.

Conditions requiring antifungal therapy are detailed as follows:

- Microbiological documentation of fungal infection
- Development of a pulmonary infiltrate
- Development of signs and symptoms of sinusitis
- Development of respiratory signs or symptoms persisting for at least 2 days (rales on auscultation, cough, localized chest pain)
- Positive nasal cultures for Aspergillus (for filamentous fungi?)
- More than 2 non contiguous sites colonized by Candida?
Galactomannan and Computed Tomography–Based Preemptive Antifungal Therapy in Neutropenic Patients at High Risk for Invasive Fungal Infection: A Prospective Feasibility Study

Johan Maertens, Koen Theunissen, Gregor Verhoef, Johnny Verschakelen, Katrien Lagrou, Eric Verbeken, Alexander Wilmer, Jan Verhaegen, Marc Boogaerts, and Johan Van Eldere

Departments of Hematology, Radiology, Microbiology, Pathology, and Medical Intensive Care, University Hospital Gasthuisberg, Leuven, Belgium

Clinical Infectious Disease 2005; 41:1242-50
GM and CT-scan based approach

All patients receive fluconazole 400 mg/day

136 episodes

117 febrile episodes

9 cases positive CT

10 positive GM antigen

19 cases for pre-emptive antifungals

19 no fever

82 defervesence

16%
136 episodes

117 febrile episodes

82 defervescence

30 persistent fever

11 unexplained relapses

41 candidates empirical antifungals

19 no fever

35%
Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Catherine Cordonnier,1 Cécile Pautas,1 Sébastien Maury,1 Anne Vekhoff,4 Hassan Farhat,11 Felipe Suarez,5 Nathalie Dhédin,6 Françoise Isnard,7 Lionel Ades,12 Frédérique Kuhnowski,8 Françoise Foulet,2 Mathieu Kuentz,1 Patrick Maisonn,3 Stéphane Bretagne,2 and Michaël Schwarzinger5,10

Clinical Infectious Diseases 2009; 48:1042–51
Study Design

- Prospective multicentric, unblinded, randomised (1:1) trial run in 12 French centers between April 2003-February 2006
- Non-inferiority trial (< 8% difference in ITT and PP)
- Statistical power 80%
- Stratifications:
  - Induction vs. Consolidation or autoSCT (alloSCT excluded)
  - AF prophylaxis (yes/no)
Endpoints

- **Primary**
  - Survival either 14 days after recovery from neutropenia or at 60 days if persistent neutropenia

- **Secondary**
  - Incidence of IFI (proven and probable according to EORTC-MSG definitions)
  - Incidence of SAE
  - Drug consumption
  - Cost
Criteria for starting AF therapy in the pre-emptive arm

- Pneumonia
- Acute sinusitis
- Mucositis grade >3
- Septic shock
- Skin lesions suggestive of IFI
- Unexplained CNS symptoms
- Periorbital inflammation
- Splenic/hepatic abscess
- Severe diarrhea
- Aspergillus colonization
- Positive GM (≥1.5) taken twice weekly

*Chest-x-rays encouraged; CT-scan performed in patients with negative chest-x-rays*
<table>
<thead>
<tr>
<th>End point</th>
<th>Empirical treatment group</th>
<th>Preemptive treatment group</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal treatment</td>
<td>92/150 (61.3)</td>
<td>56/143 (39.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Reason for starting antifungal treatment $^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated fever between day 4 and day 14 after antibacterial treatment initiation</td>
<td>55 (59.8)</td>
<td>1 (1.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (6.5)</td>
<td>26 (46.4)</td>
<td></td>
</tr>
<tr>
<td>Severe mucositis</td>
<td>8 (8.7)</td>
<td>10 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Isolated fever beyond day 14</td>
<td>11 (12.0)</td>
<td>7 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Sootic shock</td>
<td>5 (5.4)</td>
<td>3 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Positive result of galactomannan antigen test</td>
<td>2 (2.2)</td>
<td>3 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Skin lesion</td>
<td>2 (2.2)</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Sinusitis or periorbital inflammation</td>
<td>0 (0.0)</td>
<td>3 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.1)</td>
<td>1 (1.8)</td>
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Empirical v. Preemptive antifungal therapy in high risk neutropenic patients

Overall survival

- Empirical, n=150: 97.0%
- Pre-emptive, n=143: 95.0%

p=ns

Invasive fungal infections

- Empirical, n=150: 2.7%*
- Pre-emptive, n=143: 9.0%

*p<0.02
Cost of antifungal drugs, 2005 €

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal empirical therapy</td>
<td>2252 ± 4050</td>
<td>0–20,726</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antifungal preemptive therapy</td>
<td>1475 ± 3329</td>
<td>0–18,500</td>
<td></td>
</tr>
<tr>
<td>IFI (preemptive therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFI (empirical therapy)</td>
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Estimated cost of antifungal drugs if liposomal AmB had been used instead of AmB deoxycholate, 2005 €

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>4261 ± 4760</td>
<td>0–21,727</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2509 ± 4099</td>
<td>0–18,500</td>
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## Alive at study end

<table>
<thead>
<tr>
<th>End point</th>
<th>Consolidation therapy or transplantation</th>
<th>Induction therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Empirical treatment group (n = 72)</td>
<td>Empirical treatment group (n = 78)</td>
</tr>
<tr>
<td></td>
<td>Preemptive treatment group (n = 70)</td>
<td>Preemptive treatment group (n = 73)</td>
</tr>
<tr>
<td></td>
<td>Empirical treatment group (n = 72)</td>
<td>Preemptive treatment group (n = 78)</td>
</tr>
<tr>
<td></td>
<td>Preemptive treatment group (n = 70)</td>
<td>Preemptive treatment group (n = 73)</td>
</tr>
<tr>
<td><strong>P</strong> or difference (95% CI) in efficacy outcomes</td>
<td></td>
<td><strong>P</strong> or difference (95% CI) in efficacy outcomes</td>
</tr>
<tr>
<td>Duration of neutrophil count &lt;500 neutrophils/μL, days</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>11 (9–16)</td>
<td>26 (21–31)</td>
</tr>
<tr>
<td></td>
<td>12 (10–16)</td>
<td>26 (18–32)</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Consolidation

- **Emp. 100%**
- **Pre-empt 97%**
- **-2.9 (-6 to 0.4)**

### Induction

- **Emp. 95%**
- **Pre-empt 93%**
- **-1.7 (-8.0 to 4.6)**
Conclusions

- **Primary endpoint**
  - Pre-emptive therapy was non-inferior to empirical therapy in terms of survival

- **Secondary endpoints**
  - The incidence of IFI was higher in the pre-emptive therapy arm
  - Pre-emptive therapy was associated with a decreased use of antifungals
  - Pre-emptive therapy was less expensive than empirical therapy
Other findings

- There were much more IFI during induction chemotherapy than in consolidation/auto SCT
- This was probably due to longer duration of neutropenia
- “OUR STUDY SUGGESTS THAT EMPIRICAL ANTIFUNGAL TREATMENT MAY RESULT IN HIGHER SURVIVAL RATES THAN WOULD PREEMPTIVE TREATMENT AMONG PATIENTS RECEIVING INDUCTION CHEMOTHERAPY”
  This is incorrect

Correct statement should be:

“Subgroup analysis showed that non-inferiority was not demonstrated in the induction therapy subgroup”
CLINICALLY DRIVEN DIAGNOSTIC ANTIFUNGAL APPROACH IN NEUTROPENIC PATIENTS: A PROSPECTIVE FEASIBILITY STUDY


JCO 2010; 28:667-74
Clinically Driven Diagnostic Antifungal Approach in Neutropenic Patients

High risk for IFD
Neutropenic fever

Baseline Diagnostic WU

Persisting fever after 4 days
Relapsing fever after 48h defervescence
Afebrile but clinical findings suggestive of IFI

Intensive Diagnostic WU:
GM over 3 consecutive days
Chest CT scan

Negative
Follow-up and repeat (or empirical)

Positive
Treatment

Oral AmB 2.000 mg/d
2002 EORTC-MSG def.

3 groups of patients
1) High risk (no AF proph and intensive chemo)
2) Low risk (auto HSCT)
3) Other (secondary proph)

Conclusion (ECIL3)

- A diagnostic-driven antifungal strategy is “feasible”
  - Clinical + GM based strategy: overall survival as with empirical
  - ↓ use of antifungal therapy vs. empirical (↓ toxicity, interactions, resistance, costs)
  - ↑ IFI (Aspergillus, Candida) vs. empirical: “expected” as pre-emptive is based on criteria included in diagnostic definitions of IFI
    - Induction chemotherapy for AL and allo-HSCT
  - Potential for early diagnosis of IFI in absence of fever with pre-emptive approach (missed by fever-driven empirical approach)
A diagnostic-driven antifungal strategy is “feasible” but

- No defined standard criteria among studies, overlap with empirical
- Majority of studies are non-comparative/observational with pro- or retrospective analysis of single center “field experiences” based on management algorithms with +/- verified adherence
- Variable local epidemiology: differences in protected environment and use of antifungal prophylaxis
- Potential exposure to fungal pathogens during radiological work-up in non-protected environment
- Clinical impact of IFI: morbidity? Further chemotherapy? Attributable mortality?
Why I like the pre-emptive approach

- I am a doctor
- I like using my brain
- I have diagnostic tools available
- I think patients should be studied and examined and management tailored (not all patients are the same)
- I think that emotional decisions are not in the best patient’s interest
- I like multidisciplinary approaches (radiologist, pathologist, microbiologist, other, including, maybe, also the ID specialist (when he is not lost in his antiretroviral problems))
May I suggest an additional option?

- Persistent febr and neutropenia
- Perform the intensive diagnostic workup
- Start empirical antifungal
- Day 3: GM and/or glucan is negative + HRCT is negative or not suggestive
- Stop antifungals and try to make a diagnosis