Managing Mould Diseases after Stem Cell Transplant

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What does « management » mean?

• Anticipate

• Diagnose

• Treat

*But first, know the ennemy*
Moulds?
A long list ....

- Aspergillus
- Zygomycetes: _Rhizopus sp. Mucor sp., Lichteimia sp., Rhizomucor, Cunninghamamella, Apophysomyces elegans, Saksenae sp. etc…_
- Fusarium
- Scedosporium
- Pseudallescheria boydii
- Acremonium ...
Know the enemy

Fungi are many

Zygomycosis

Aspergillosis

Fungi are everywhere

Fusariosis and some others
Anticipate

- **Who** are the patients at risk?
- **When** is the risk?
- According to the answers, what can we do? *How and when?*
Moulds = 73% of the total IFI after HSCT
Different risks in different HSCT

Prospective data from the TRANSNET, 2001-2006
Network of 23 US centers, 875 HSCT recipients, 983 IFI
Kontoyiannis DP, et al. CID 2010

Cumulative incidence curves for any IFI among HSCT recipients in the TRANSNET surveillance cohort, stratified by type of HSCT.
### SAIF-1 (2005-2007)

<table>
<thead>
<tr>
<th>Species</th>
<th>% (n=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus</td>
<td>85</td>
</tr>
<tr>
<td>A. flavus</td>
<td>4</td>
</tr>
<tr>
<td>A. nidulans</td>
<td>3</td>
</tr>
<tr>
<td>A. terreus</td>
<td>2</td>
</tr>
<tr>
<td>A. niger</td>
<td>4</td>
</tr>
<tr>
<td>A. ustus</td>
<td>0.5</td>
</tr>
<tr>
<td>A. versicolor</td>
<td>0.5</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
</tr>
</tbody>
</table>

### SAIF-2 (2008-2010)

- A. fumigatus (83%)
- A. flavus (7%)
- A. nidulans (3%)
- A. terreus (2%)
- A. niger (1%)
- Autre (3%)

*Lortholary et al CMI 2011*
Is it useful to know about the species of Aspergillus?

- *A. terreus* $\Rightarrow$ R to ampho B
- *A. lentulus* $\Rightarrow$ R to azoles
Mould infections: classically the lung is the main route of infestation
Sinus, nose, and orbitis: always suspect of IMI (Mucor or Aspergillus) in a patient at risk

Courtesy of Patricia Ribaud
Mould infections: classically the lung as the main route of infestation, but moulds are very inventive

- Mucormycosis outbreak associated with hospital linens: 5 cases in different wards of the hospital, the same *Rhizopus delemar* in the patients and on 42% of the clean linens, 5 deaths. 
  
  *Duffy J et al. Pediat Infect Dis J 2014*

- Outbreak of intestinal infection due to *Rhizopus microsporus*: 12 cases of gut infection in hematology patients. Suspected source: prepackaged ready-to-eat food items, wooden chopsticks, and allopurinol tablets. 6 deaths. 
  
  *Cheng VCC et al. JCM 2009*
Some unusual presentations of invasive aspergillosis

Female patient, 65 y, AML, relapse Cutaneous aspergillosis developed on the insertion site of the catheter
Male patient, 66 y, AML induction, deep neutropenia. Primary cutaneous aspergillosis.

Kazan et al. CMI 2010
But initially: onychomycosis due to Fusarium
Male patient, 68y, acute transformation of essential thrombocythemia evolving since 25 years. High-dose chemo.
At the end of the aplasia, he developed headaches and visual troubles leading to MRI Sphenoidal and cerebral abcess involving brain and optical nerve
Sinus biopsies: **invasive aspergillosis**
IMI in a HSCT recipient:
What does it mean?
Survival FROM aspergillus diagnosis in allogeneic SCT

Martino R et al. Spain
Br J Haem 2003

Control (n=358), 55%
Non candida IFI (n=37), 20%

Marr K et al - Seattle
CID 2002

1-year survival after proven and probable infection

Cordonnier et al. France
EBMT 2002
Mucormycosis after allogeneic HSCT: a French Multicentre Cohort Study (2003–2008)
Overall survival FROM diagnosis

Xhaard et al, CMI 2012
When is the risk after SCT?

Prospective data from the TRANSNET, 2001-2006
Network of 23 US centers, 875 HSCT recipients, 983 IFI

Distribution of time to invasive fungal infection (IFI) stratified by infection type (all IFI cases in surveillance cohort)

Parameters which may influence the risk of IMI in HSCT patients

Classical risk factors
- Underlying disease
- Duration of neutropenia
- Type of transplant
- GVHD
- Steroids
- Other IS therapies

Genetic factors
- TLR4, TLR5
- MBL ....

Environmental factors
- Geography
- Climate/Season
- LAF room

Incidence of IMI in a given center

Prophylaxis

Diagnostic energy!!

Empirical or preemptive strategy for neutropenic pts?

Previous IFI

Diagnostic energy!!
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Aspergillus</th>
<th>Mucormycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed engraftment or secondary neutropenia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extensive cGVHD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CMV infection</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Steroids</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Relapse</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Iron overload</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td>+ ?</td>
</tr>
</tbody>
</table>

Kontoyiannis D 2005; Garcia-Vidal C 2008
Mucorales after HSCT
Selection pressure of antifungals?

Initially reported with voriconazole
(Garcia-Vidal C 2008; Marty F 2004; Trifilio SM 2007; Pongas G 2009)

But…..

• The increased incidence of mucor started before vori
• Not found with vori in other series (Torres-Narbona 2008, Maron G 2013)
• Prospective comparison of Vori vs Fluco : 2/295 vs. 3/305 mucor (Wingard 2010)
• Also reported with posa (Kishel JJ 2008; Kleinotiene G 2013; Lekakis LJ 2009; Lerolle N 2014, Schlemmer F 2008)
• Breakthrough cases of mucor also reported under candins (Suzuki K 2009; Pang KA 2012)

Reviewed in Robin C et al, Current Op Hematol, in press
Aspergillus or Mucor? 
That is the question

Diagnosis and treatment
DIAGNOSE

Clinic

Imaging

Biology:

- Classical methods: biopsy + culture + immunochemical techniques + PCR

- Non-culture based: GM, BD-glucan, PCR
Aspergillus or Mucor?

CLINIC

**Lung**: mainly aspergillus
BUT the most frequent site of infection in mucor in hematology patients

**Rhino-orbital-cerebral lesion**: more likely mucor in hematology patients
BUT aspergillus too
Aspergillus or Mucor?

IMAGING

EORTC-MSG criteria: no distinction between both
During neutropenia, early in lung:

The halo sign: more likely aspergillus, but also mucor, pulmonary embolism, tuberculosis, CMV, legionella, nocardia etc....

The reversed halo sign: more likely zygo, but also mucor, tuberculosis, paracoccidioidomycosis, Wegener etc....

Both evolve to dense nodules and cavitation after neutrophil recovery

Images from a 49-year-old woman who presented with febrile neutropenia during treatment for recurrent AML

### Galactomannan and 1,3-β-D-Glucan spectra

<table>
<thead>
<tr>
<th></th>
<th>Galactomannan*</th>
<th>1,3-β-D-Glucan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida sp.</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Aspergillus sp.</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Zygomycosis</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fusariosis</td>
<td>+/-*</td>
<td>+</td>
</tr>
<tr>
<td>Trichosporon</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

* And also: Alternaria, Cladosporium, Fusarium oxysporum*, Penicillium, Trichophyton etc…. 
Galactomannan: recommendations for a strategy in adults

- Prospective monitoring of serum is a feasible approach for adult neutropenic patients undergoing intensive chemotherapy for leukemia or receiving an allogeneic stem cell transplantation for the early diagnosis of invasive aspergillosis (AII) [Note: Plasma may also be used (CIII)]

- Galactomannan monitoring is recommended every three to four days for patients admitted to hospital (AII)

- Persistent galactomannan antigenaemia during therapy is a poor prognostic sign and should prompt a reassessment of the management of the patient (BII)

- A diagnostic driven strategy that incorporates galactomannan monitoring should be combined with high resolution CT imaging, appropriate clinical and microbiological evaluation to diagnose invasive aspergillosis early. A single sample with a galactomannan index of ≥0.7 or 2 consecutive samples with an index of ≥0.5 should prompt a thorough diagnostic work-up (AII)
Galactomannan: recommendations for use in adults

- The manufacturer recommends a cut-off of 0.5 for the Platelia Aspergillus in serum

- Detection of galactomannan in BAL fluid can be used to support the diagnosis of invasive aspergillosis in neutropenic and non-neutropenic patients. Pending a recommended cut off by the manufacturer, a cut-off of 1.0 is recommended (BIII)

- Detection of galactomannan in CSF can support the diagnosis of central nervous system aspergillosis. Pending a recommended cut-off by the manufacturer, a cut-off of 0.5 is recommended (BIII)

- Experience with galactomannan detection in pleural fluid, sputum or urine is insufficient to make recommendations (CIII)
1,3 β-D glucan test is sofar...

- An indirect test with a broader fungal spectrum than GM, but with also many false positives (bacterial infections, IVIG, albumine, hemodialysis etc…)

- An expensive test

- A microbiological criteria for probable IFI in the 2nd version of the EORTC-MSG definitions (B De Pauw CID 2008)

- In the ECIL guidelines: considered for screening in high-risk neutropenic patients (BII)*

* Marchetti O, et al. BMT 2011
Aspergillus PCR: still not really in the game for diagnosis

PCR recommendations

The current status of the technical and clinical validation of PCR for Aspergillus in blood and other fluids does not currently allow for a recommendation for clinical use.

The technical recommendations of the European Aspergillus PCR Initiative (EAPCRI) for processing aspergillus PCR have been published after the ECIL 3 meeting and are those recommended by ECIL.

Aspergillus PCR: one step closer towards standardisation
L White, S Bretagne, L Klingspor, WJG Melchers, E McCulloch, B Schulz, NFinnstrom, C Mengoli, RM Barns, JP Donnelly, J Loeffler
Mucor PCR as a promising tool for early treatment of mucormycosis in high-risk patients

Using 3 independent RT-PCR (Lichteimia spp., Rhizopus spp. + Mucor spp., and Rhizomucor spp.)

10 patients

Diagnosis on serum 68 to 3 days before histological diagnosis
TREAT ASPERGILLOSIS
### Guidelines for the Management of Invasive Aspergillosis

#### First-Line Therapy

<table>
<thead>
<tr>
<th>IDSA, CID 2008</th>
<th>ECIL update 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voriconazole IV or PO</strong> AI</td>
<td><strong>Voriconazole IV or PO</strong> AI</td>
</tr>
<tr>
<td>(Seriously ill: IV: A-III)</td>
<td>(Initiation with the oral form: C-III)</td>
</tr>
<tr>
<td><strong>AmBisome 3 mg/kg</strong> AI</td>
<td><strong>AmBisome 3 mg/kg</strong> BI</td>
</tr>
<tr>
<td>(alternative in some patients)</td>
<td></td>
</tr>
<tr>
<td><strong>Combination not recommended</strong> BII</td>
<td><strong>Combination Vori+anidula</strong> * CI</td>
</tr>
<tr>
<td></td>
<td><strong>Abelcet</strong> BII</td>
</tr>
<tr>
<td></td>
<td><strong>Caspofungin</strong> CII</td>
</tr>
<tr>
<td></td>
<td><strong>Itraconazole (start IV)</strong> CIII</td>
</tr>
<tr>
<td></td>
<td><strong>ABCD</strong> CI</td>
</tr>
<tr>
<td></td>
<td><strong>L-Ampho B « against the use »</strong> AI</td>
</tr>
</tbody>
</table>

**If breakthrough aspergillosis** under mould-active azole prophylaxis: switch to another drug class: BIII

**Duration of treatment:** $\geq 6$-$12$ weeks

**Breakthrough infection:** not addressed

**Duration of treatment:** no recommendation; go on till CR and immunosuppression recovery

*Provisionnal, pending full publication*
Voriconazole vs. L-ampho B

Complete+partial response

Survival

Herbrecht et al. NEJM 2002
First line, proven or probable aspergillosis

Voriconazole: 6 mg/kg IV x 2/j at d1, then 4 mg/kg IV x 2/d
Anidulafungin: 200 mg IV d1, then 100mg/d

For 2 to 4 weeks

Possibility of switch to oral vori from d14

Total duration of study treatment: 6 weeks

Primary objective: overall survival at 6 weeks

K Marr, et al. ESCMID 2012

Poster presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), London, UK, 31 March – 3 April 2012
A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis.
A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Voriconazole monotherapy</th>
<th>Combination therapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (week 6), n (%)</td>
<td>39 (27.5)</td>
<td>26 (19.3)</td>
<td>0.0868</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (week 12), n (%)</td>
<td>55 (39.4)</td>
<td>39 (29.3)</td>
<td>0.0766</td>
</tr>
<tr>
<td>Death due to IA (week 6), n (%)</td>
<td>33 (23.9)</td>
<td>23 (17.3)</td>
<td>0.2058</td>
</tr>
<tr>
<td>Global response – success, n (%)</td>
<td>61 (43)</td>
<td>44 (32.6)</td>
<td>0.0782</td>
</tr>
<tr>
<td>Complete response</td>
<td>17 (12)</td>
<td>8 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>44 (31)</td>
<td>36 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Stable response</td>
<td>19 (13.4)</td>
<td>26 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>7 (4.9)</td>
<td>8 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Death, probable IA, n (%)</td>
<td>39 (14.3)</td>
<td>24 (8.8)</td>
<td>0.0504</td>
</tr>
<tr>
<td>Death, probable IA – GM only³</td>
<td>30 (27.3)</td>
<td>17 (15.7)</td>
<td>0.0372</td>
</tr>
</tbody>
</table>

Poster presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), London, UK, 31 March – 3 April 2012
MUCOR
# Mucormycosis
What’s specific in HSCT recipients?

<table>
<thead>
<tr>
<th>Region, country</th>
<th>Reference</th>
<th>Design</th>
<th>Period</th>
<th>No. Cases/ No.HSCT</th>
<th>Prevalence of mucormycosis in alloHSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>Garcia-Vidal <em>CID</em> 2008</td>
<td>Retrospective, FHCRC</td>
<td>1998-2002</td>
<td>5/1248</td>
<td>0.4%</td>
</tr>
<tr>
<td>USA</td>
<td>Park <em>Emerg Inf Dis</em> 2011</td>
<td>Transnet, prospective</td>
<td>2001-2005</td>
<td>44/15 820</td>
<td>0.3% (0.85% in HLA-mismatched related donors)</td>
</tr>
<tr>
<td>France</td>
<td>Xhaard <em>CMI</em> 2012</td>
<td>Retrospective, national</td>
<td>2003-2008</td>
<td>29/7097</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Mucormycosis
What’s specific in SCT recipients?

The timing

Transnet 2001-2006
Aspergillosis, and then Mucor??
Why Mucor \textit{after} Aspergillus in HSCT?

- Different risk factors? …and subsequent different timings
- Survival to aspergillosis after HSCT selects the more immunodepressed patients?
- Selection pressure under voriconazole given for a previous aspergillosis?
- Concomitant exposure and mixed infection, but overgrowth of aspergillus in the lab?
- Late diagnosis because no indirect biomarker?
TREAT MUCORMYCOSIS

ECIL guidelines at: www.kobe.fr/ecil

and

Skiada et al. Haematologica 2013; 98(4)
No evidence that identification of the causative Mucorales to the genus and/or species level led to guide antifungal treatment [4].

Species identification important for outbreak-investigations [5].

The differentiation between Mucorales and Non-Mucorales infection is of importance as it has major therapeutic implications. ….

Posaconazole

- 96 cases collected in a case-report revision
  - 67 cases plus surgery
  - 2 cases only posaconazole
  - 39 cases posaconazole plus lipid compound of AmB

- Response
  - Complete response: 62 (64%)
  - Partial response: 7 (7%)
  - Stable: 1 (1%)

No impact on grading

Combination treatment

- Review of 32 cases (hematological diseases only) from the SEIFEM and FUNGISCOPE registries treated with a combination of posaconazole with a lipid formulation of amphotericin B (ABLC, n=5; liposomal amphotericin B, n=27)
- Posaconazole was mainly used as salvage treatment
- Response rate: 56%

**Mucormycosis**  
**Recommendation for first line (part 1)**

Management includes antifungal therapy, control of underlying conditions and surgery

<table>
<thead>
<tr>
<th>Antifungal therapy</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB deoxycholate</td>
<td>C II</td>
</tr>
<tr>
<td>Liposomal AmB</td>
<td>B II</td>
</tr>
<tr>
<td>ABLC</td>
<td>B II</td>
</tr>
<tr>
<td>ABCD</td>
<td>C II</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>C III²</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>C III</td>
</tr>
</tbody>
</table>

1. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure.
2. No data to support its use as first line treatment. May be used as an alternative when amphotericin B is absolutely contraindicated.
Mucormycosis
Recommendation for first line (part 2)

Management includes antifungal therapy, control of underlying conditions and surgery.  

<table>
<thead>
<tr>
<th>Control of underlying condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>A II</td>
<td></td>
</tr>
</tbody>
</table>

Surgery

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>- rhino-orbito-cerebral</td>
<td>A II</td>
</tr>
<tr>
<td>- soft tissue</td>
<td>A II</td>
</tr>
<tr>
<td>- localized pulmonary lesion</td>
<td>B III</td>
</tr>
<tr>
<td>- disseminated</td>
<td>CIII4</td>
</tr>
</tbody>
</table>

Hyperbaric oxygen CIII

---

3 Control of underlying condition includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy

4 Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Surgery in Mucor is crucial

- To reduce the fungal burden
- To improve penetration of antifungals in the tissues

- Should be as early as possible
- Should be mostly repeated
Mucormycosis
Recommendation for maintenance therapy or in case of intolerance to first line therapy

Maintenance therapy (prior response or stable disease)
Or intolerance to first line therapy

Posaconazole

B II

1 whenever possible, overlap of a few days (at least 5) with first line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated
The main questions for the future

How to reduce the risk?
- get epidemiological data in specific populations
- develop scoring system taking in account local epidemiology and individual risk factors
- prophylaxis

How to intervene early?
- early biological markers
- systematic screening in high-risk populations
- identify part of the risk through genetic markers?

Consider antifungals as only a BRIDGE to immune recovery
- reverse immunosuppression
- augment the immune system
Conclusion

Clinic is crucial

Imaging helps but never gives a mycological diagnosis

Be invasive to get the diagnosis

Repeat the investigations each time necessary

Precise identification of IFI is essential for treatment