

55-year old female with MDS who received in september 2009 an Allogeneic HSCT from a MUD

Supportive care: fluconazole+GM twice/w, acyclovir, levofloxa.

## POST-TRANSPLANT CLINICAL COURSE

day +3: WBC 160, ANC 140

Fever

negative Blood Culture  
*Galactomannan* 0.05  
chest xRay neg



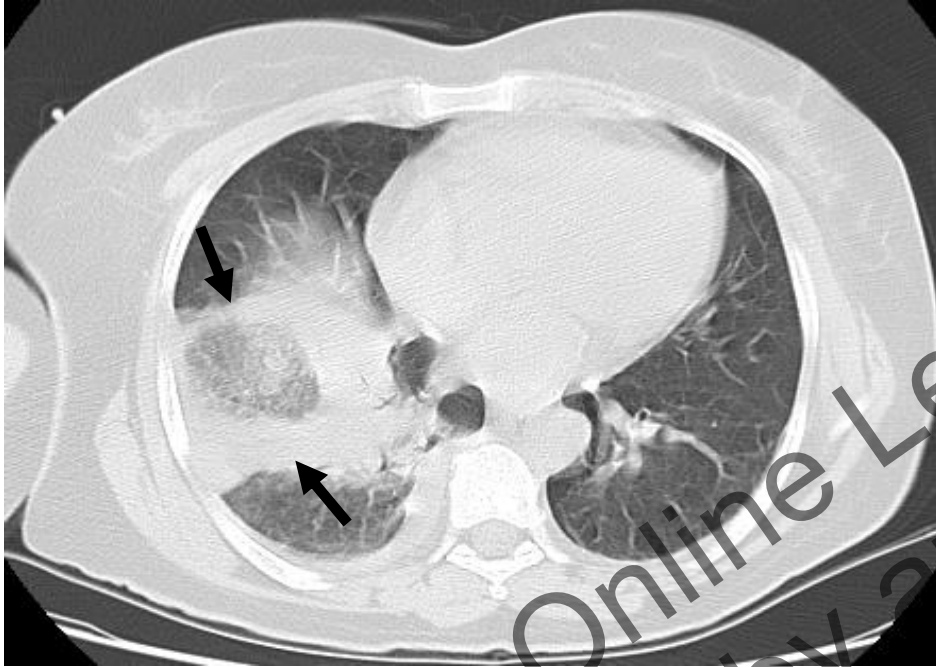
PIPERA-TZB  
Teicoplanin

day +6: Persistent Fever  
pain at right shoulder  
basal crackles in right lung



CT scan

# day +6: post-transplant



WBC 20

Galactomannan 0,14

## Chest CT scan

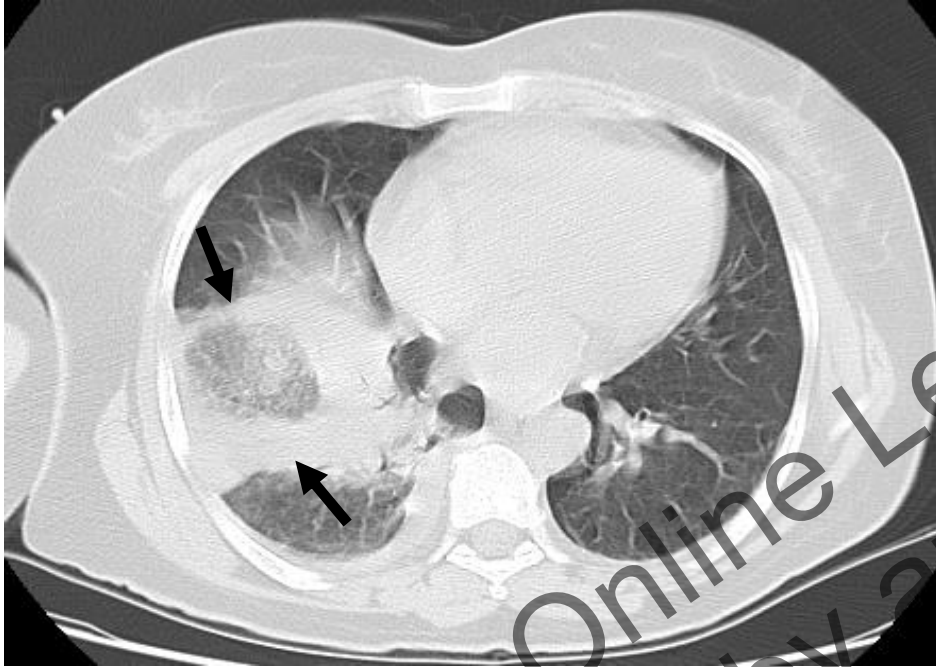
In the right lung presence of a focal ground-glass opacity mass surrounded by a solid ring



# Which approach would you recommend?

- 1) **Modify ATB**
- 2) **add antifungal therapy**
- 3) **BAL**
- 4) **biopsy**

# day +6: post-transplant

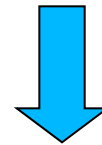


WBC 20

Galactomannan 0,14

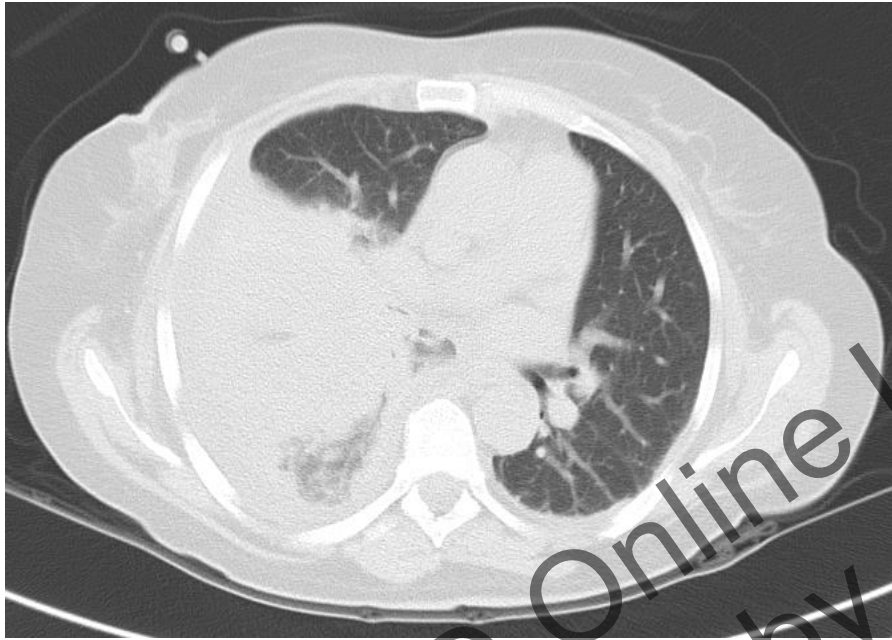
## Chest CT scan

In the right lung presence of a focal ground-glass opacity mass surrounded by a solid ring



**Liposomal AmB 3 mg/Kg**

# day +16: post-transplant



## Engraftment

WBC 1280/mm<sup>3</sup>, ANC 990  
AST 38, ALT 51, bilirubin 18  
Galactomannan 0,21

**Steroid 2 mg/Kg suspected hepatic GVHD**

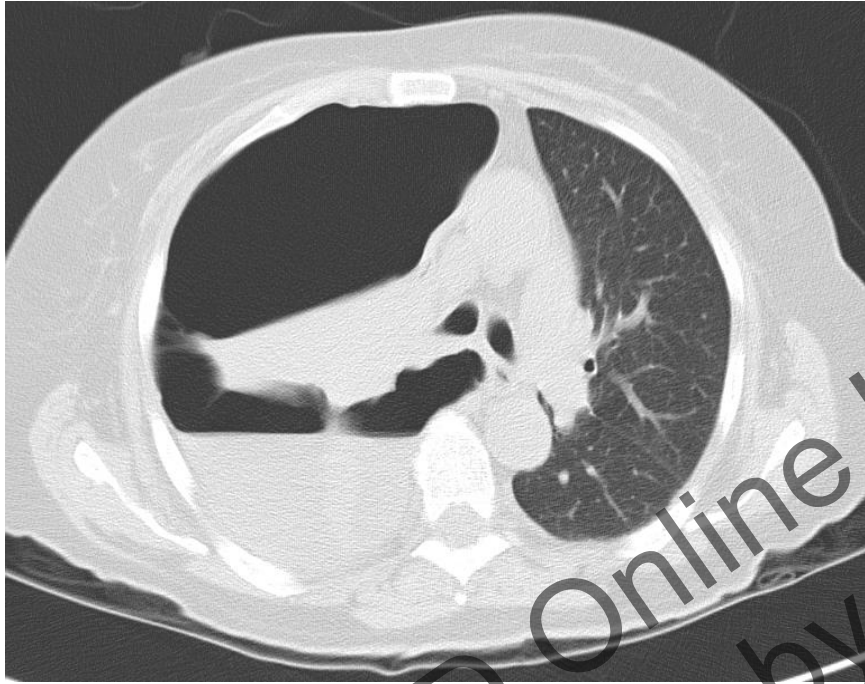
**Liposomal AmB 3 mg/Kg/d**

## **Chest CT scan:**

- On the right lung large pleural effusion reaching the upper part of the lung



# day +29: post-transplant



WBC 2490

ANC 1960

Galactomannan 0,15

## Chest CT scan:

- In the right lung, large **pneumothorax** with collapse of the entire upper and middle lobe, presence of pleural effusion
- The mediastinal structures are slightly deviated to the left part

# day +29: post-transplant

***Tube thoracostomy***: 450 ml of *pleural* effusion

## ***BAL & pulmonary biopsy***

Galatomannan 0.15

culture: Rhizopus

Sequencing: Rhizopus microsporus

# Which treatment would you recommend?

- 1) Increase the dose of L-AmB
- 2) Combine L-AmB with caspofungin
- 3) Combine L-AmB with posaconazole
- 4) Combine L-AmB with deferasirox



# day +29: post-transplant

***Tube thoracostomy***: 450 ml of *pleural* effusion

## ***BAL & pulmonary biopsy***

Galatomannan 0.15

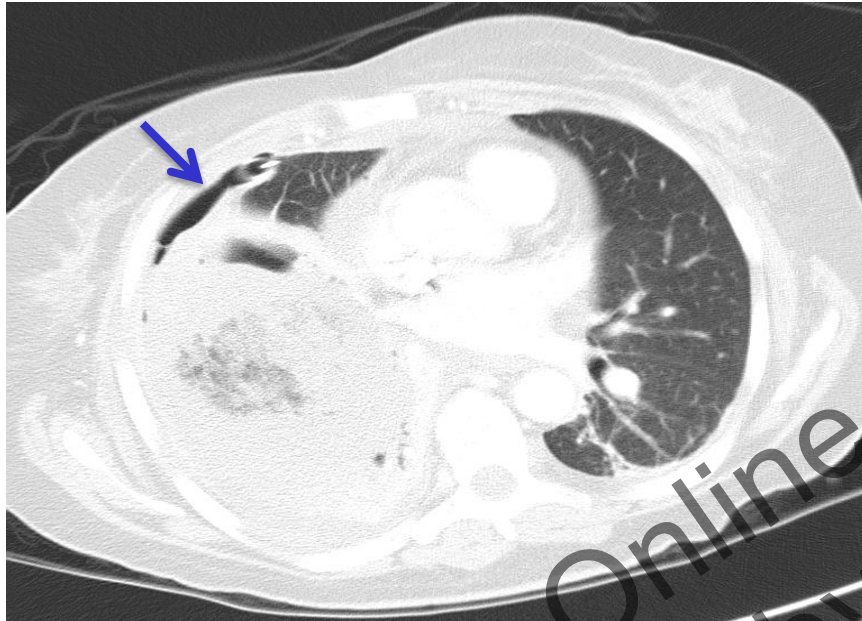
culture: Rhizopus

Sequencing: Rhizopus microsporus



**Liposomal AmB 5 mg/kg + caspofungin + deferasirox**

# day +30: post-transplant



WBC 4230  
ANC 3490

## Chest CT scan

- In the right lung, re-expansion of pulmonary parenchyma of the previously collapsed upper lobe
- In the right lung large pleural effusion which compress pulmonary parenchyma of middle and inferior lobes of the right lung; it remains a thin area of pneumothorax and pleural collection attached to the chest wall
- in the left lung presence of the round nodules



**Day +36**

**CT scan: progressive increase of the pulmonary lesions**



**critical evaluation with the Thoracic Surgery Team of the possibility of a radical right pneumectomy**

**PRO: radical intervention of the lesion with increased chance to cure the fungal infection**

**CONS: thrombocytopenia  
concomitant immunosuppression, GVHD:  
possibility of new infections  
poor general condition of the patient**

**Day +49: exitus**

## ESCMID<sup>†</sup> and ECMM<sup>‡</sup> joint clinical guidelines for the diagnosis and management of mucormycosis 2012

**TABLE 8.** Recommendations on targeted first-line treatment of mucormycosis in adult patients

Population	Intention	Intervention	SoR	QoE	Comment	References
Any	To increase survival rates	Surgical debridement	A	IIu	n = 32 n = 90 n = 45 n = 9 n = 59 n = 92, paediatric	120 3 38 7 25 121
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	IIu	n = 470 n = 19 n = 90 n = 92, paediatric	3 122 7 121
Immunocompromised	To increase survival rates	Immediate treatment initiation	A	IIu	n = 70	27
Any	To cure and to increase survival rates	Amphotericin B, liposomal 25 mg/kg <sup>a</sup>	A	IIu	n = 4 n = 16 n = 5 n = 21 n = 28 n = 130 n = 40 Animal model	105 196 128 26 152 7 57 124
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days <sup>a</sup>	A	II	Animal model	127
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg <sup>a</sup>	B	IIu	Animal model n = 10 n = 7 Animal model Animal model	126 130 7 126 127
Any	To cure	Posaconazole 4 × 200 mg/day or 2 × 400 mg/day <sup>a</sup>	B	IIu	n = 8 n = 17 Animal model	26 7 131
Any	To cure	Lipid-based amphotericin plus caspofungin <sup>a</sup>	C	III	n = 7	135
Any	To cure	Amphotericin B, deoxycholate, any dose <sup>a</sup>	D	I	Renal toxicity n = 9 n = 532 Renal toxicity n = 10 n = 21	137 105 3 136 38 7

CNS, central nervous system; QoE, quality of evidence.

<sup>a</sup>Treatment duration is determined on a case-by-case basis and depends, for example, on extent of surgery and organs involved.

# ECIL-5: MUCORMYCOSIS Combination treatment

Review of 32 cases from the SEIFEM and FUNGISCOPE registries treated with a combination of posaconazole with a lipid formulation of AmB (ABLC =5, liposomal AmB=27). *Pagano L, Cornely O, Busca A. Haematologica 2013*

Posaconazole was mainly used as salvage treatment

Response rate: 56%

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1556-1558

0066-4804/08/\$08.00+0 doi:10.1128/AAC.01458-07

Copyright © 2008, American Society for Microbiology. All Rights Reserved.

Vol. 52, No. 4

## Combination Echinocandin-Polyene Treatment of Murine Mucormycosis<sup>∇</sup>

Ashraf S. Ibrahim,<sup>1,2\*</sup> Teclegiorgis Gebremariam,<sup>1</sup> Yue Fu,<sup>1,2</sup>  
John E. Edwards, Jr.,<sup>1,2</sup> and Brad Spellberg<sup>1,2</sup>

rg,<sup>2,3</sup>

# ECIL-5: MUCORMYCOSIS

## Recommendation for First line

Combination therapy: **C III**

## Recommendation for salvage therapy

Combination Lipid AmB and Caspo: **B III**

Combination Lipid AmB and Posa: **B III**

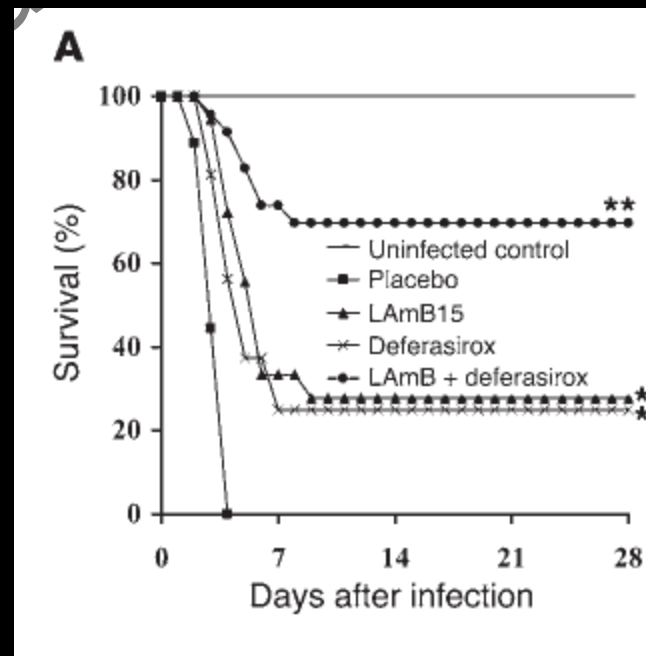
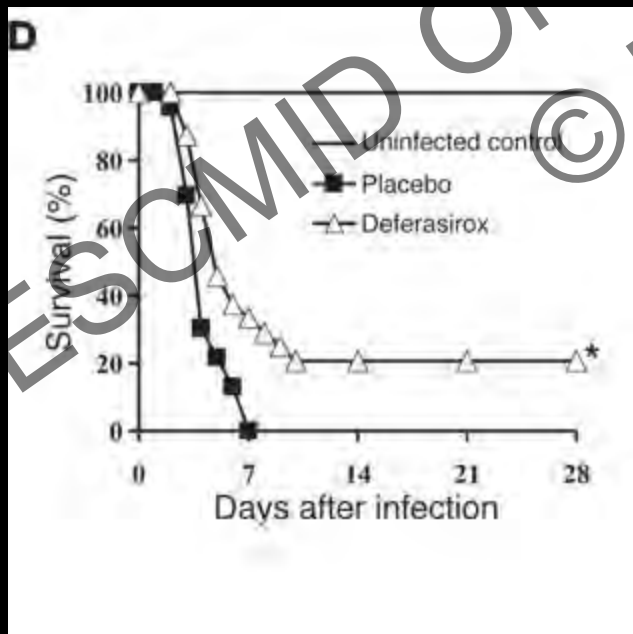


# MUCORMYCOSIS

## IRON CHELATION THERAPY (“Iron starvation”)

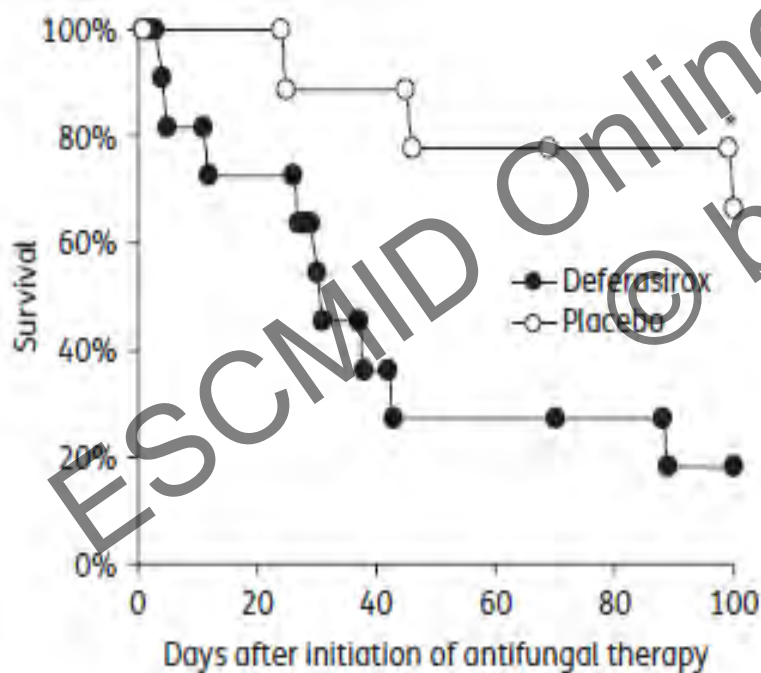
The iron chelator deferasirox protects mice from mucormycosis through iron starvation

Ashraf S. Ibrahim,<sup>1,2</sup> Teclegiorgis Gebermariam,<sup>1</sup> Yue Fu,<sup>1,2</sup> Lin Lin,<sup>1</sup>  
Mohamed I. Hussein,<sup>1</sup> Samuel W. French,<sup>1,3</sup> Julie Schwartz,<sup>4</sup>  
Christopher D. Skory,<sup>5</sup> John E. Edwards Jr.,<sup>1,2</sup> and Brad J. Spellberg<sup>1,2</sup>



# The Deferasirox–AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial

Brad Spellberg<sup>1,2\*</sup>, Ashraf S. Ibrahim<sup>2,3</sup>, Peter V. Chin-Hong<sup>4</sup>, Dimitrios P. Kontoyiannis<sup>5</sup>, Michele I. Morris<sup>6</sup>, John R. Perfect<sup>7</sup>, David Fredricks<sup>8</sup> and Eric P. Brass<sup>2,9</sup>



<u>characteristics</u>	<u>L-AmB+ DFX</u>	<u>L-AmB +placebo</u>
<b>No. patients</b>	<b>11</b>	<b>9</b>
<b>Active malignancy</b>	<b>7 (74%)</b>	<b>3 (33%)</b>
<b>Concomitant antifungal Tx</b>	<b>6 (55%)</b>	<b>7 (78%)</b>

# Take home messages

- ✓ The presence of 'reversed halo sign' may be suggestive of mucormycosis (19% in mucorm., <1% asperg.) (in particular when associated with neg GM)
- ✓ Early treatment of mucormycosis is extremely important
- ✓ Surgery should be considered, whenever feasible
- ✓ Liposomal AmB at the dose of 5-10 mg/Kg is treatment of choice
- ✓ Combination treatment may be considered for high risk patients