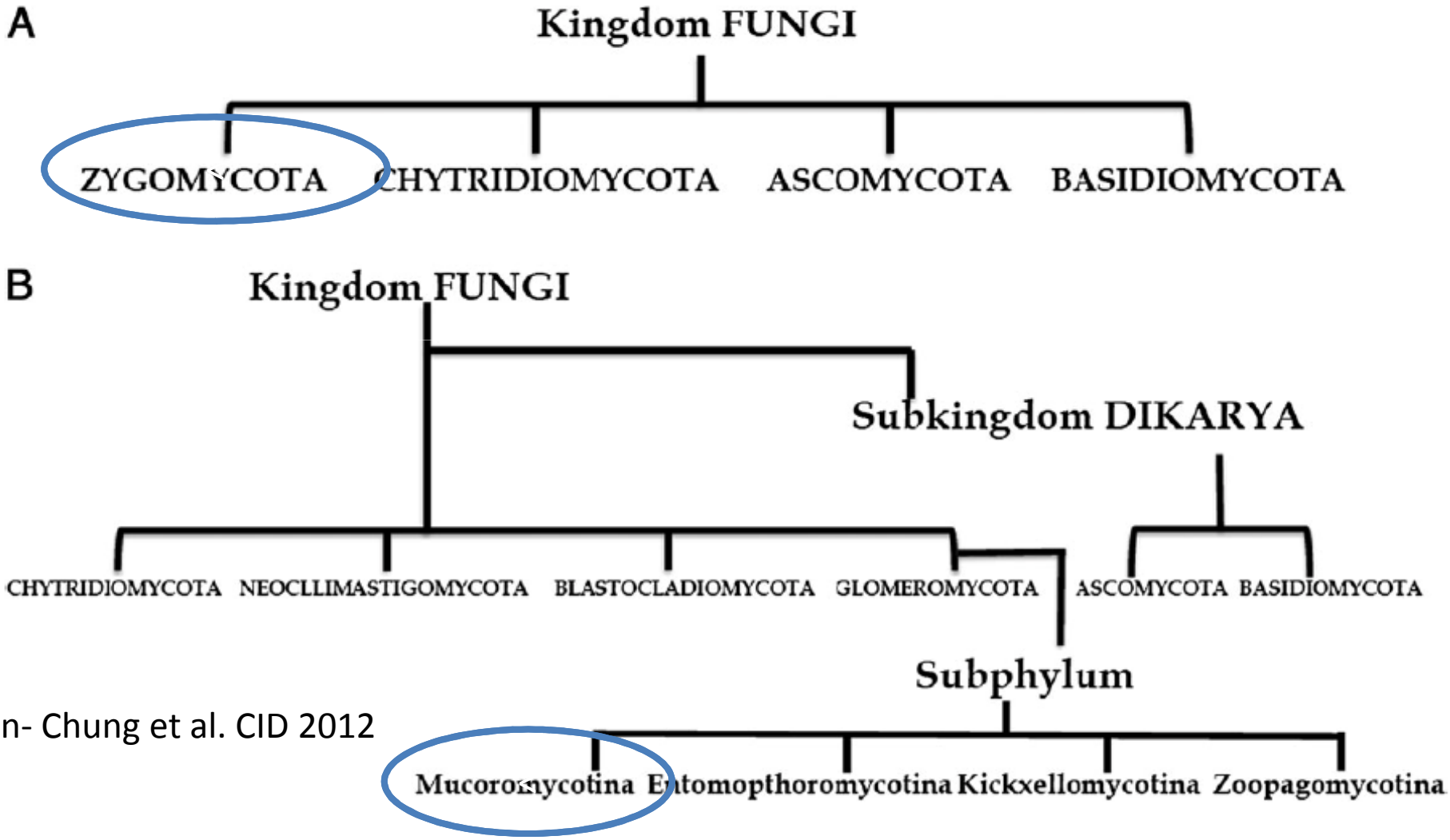
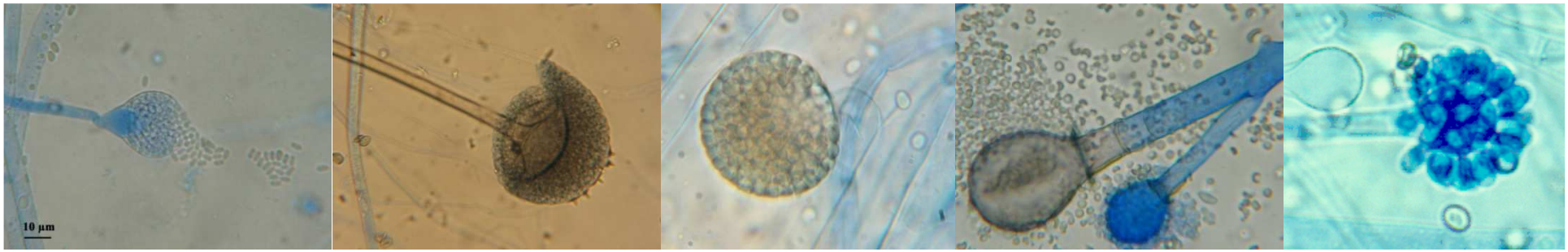
# Zygomycoses n'existent plus….!




Kwon- Chung et al. CID 2012

**Figure 1.** Old (*A*) and a proposed new (*B*) classification schemes of the kingdom Fungi.




# Epidemiology and treatment of mucormycosis

**Olivier Lortholary, M.D.; Ph.D.**

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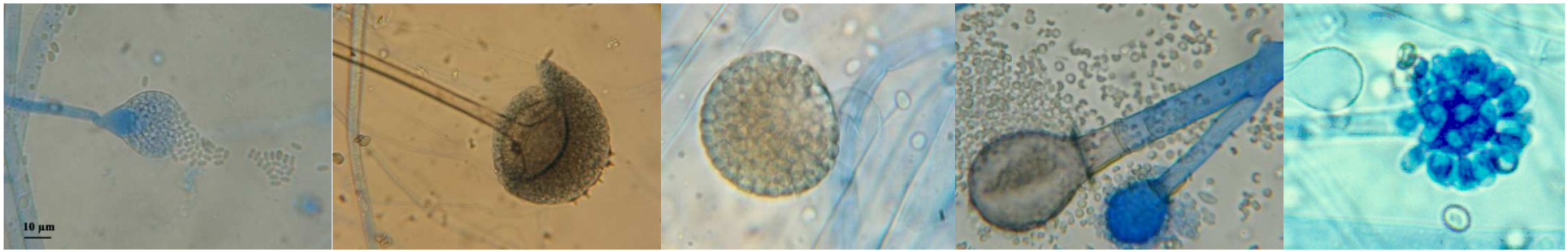


# Epidemiology of mucormycosis

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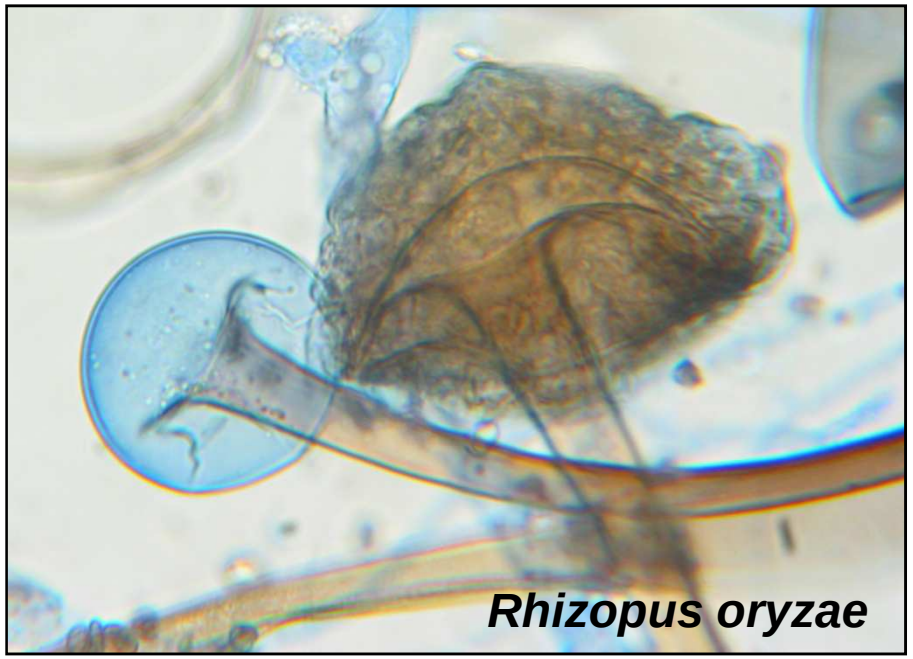
# Ecology

- ✓ Filamentous fungi with broad, thin walled, sparsely septate , « ribbon-like » hyphae




- ✓ Ubiquitous (hospital/home !)
- ✓ Saprophytic fungi
  - soil
  - decaying material
  - fruits
- ✓ Sporulation ++, air-borne transported spores
- ✓ → Respiratory tract colonization/infection [also GI tract/skin]

# Increasing Incidence of Zygomycosis (Mucormycosis), France, 1997–2006

Dounia Bitar, Dieter Van Cauteren, Fanny Lanternier, Eric Dannaoui, Didier Che, Francoise Dromer, Jean-Claude Desenclos, and Olivier Lortholary

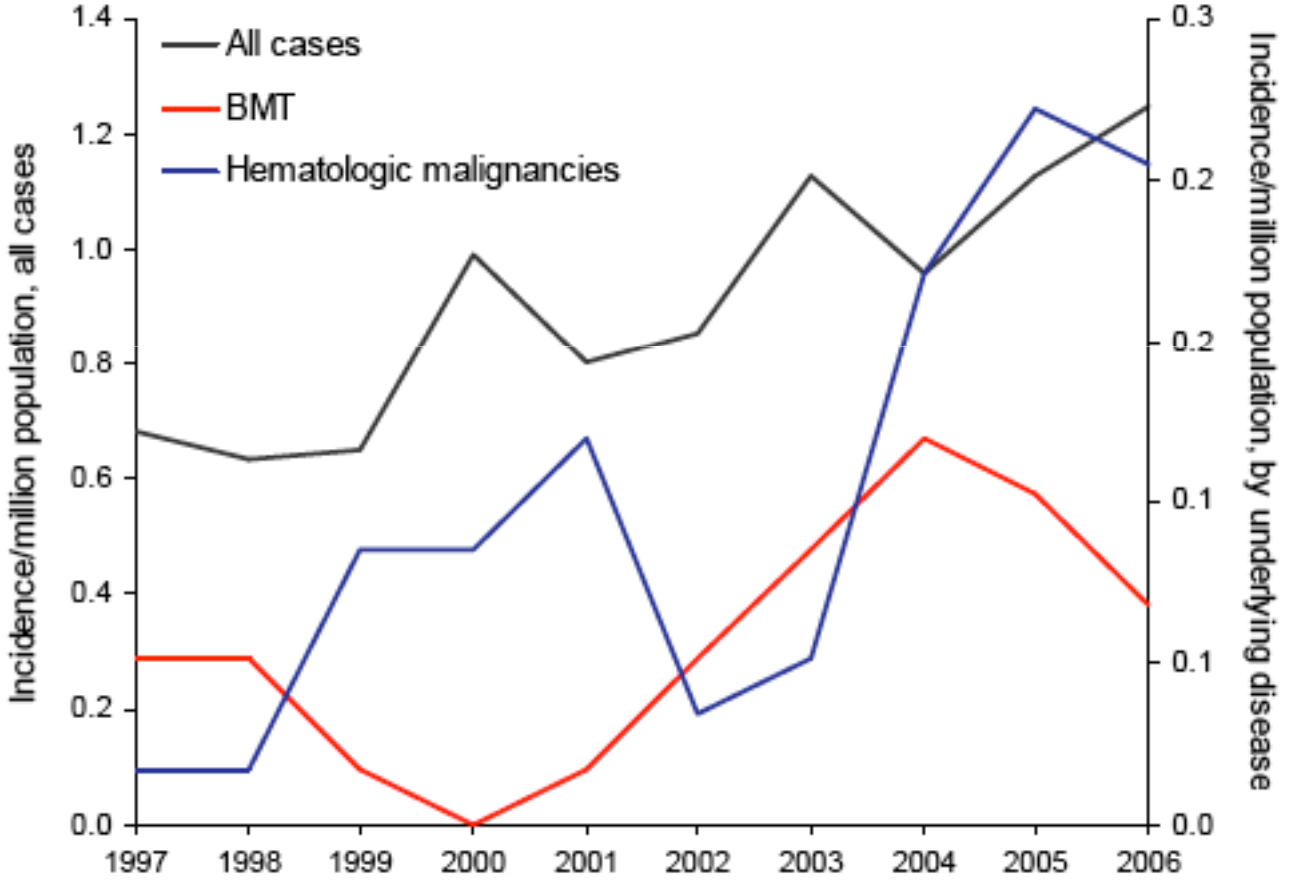



Figure 1. Evolution of the incidence of zygomycosis, France, 1997–2006. BMT, bone marrow transplantation.

*Emerg Infect Dis Sept 2009*

# Mucormycosis burden in France 2001-2010

- Among 35,876 incident IFIs in French hospital data base : 1.5% mucormycosis
- Incidence increased over time (+7.3% per year; P<0.001)
- Lethality increased by 9.3% (P= 0.03)

Bitar et al. Unpublished data

# Risk factors in mucormycosis

## Host-related

- Haematological malignancies with/ without HSCT
- Prolonged/severe neutropenia
- Diabetes uncontrolled with/ without ketoacidosis
- Iron overload
- Major trauma
- Prolonged use of corticosteroid
- Intravenous drug abusers
- Neonatal prematurity
- Malnourishment
- Voriconazole/caspofungin therapy

## Environment-related

- Heavy air fungal load
- Contaminated air filter
- Healthcare-related procedures & devices (contaminated wound dressings, transdermal nitrate patches, intra-venous catheters, tongue depressor, allopurinol pills)

Petrikkos G *et al.* CID 2012; 54 (Suppl 1): S23-34

# Risk factors in mucormycosis

| Reference | Count-ries | Period | Cases No. | HM (%) | DM (%) | SOM/ SOT | DFO (%) | HIV (%) | AI/ CO | Trauma/ no |
|---|---|---|---|---|---|---|---|---|---|---|
| Roden, 2005 | Global | 1885-2004 | 929 | 21 | 36 | 7 | 6 | 2 | 1 | 19 |
| Bitar, 2009 | France | 1997-2006 | 63 | 17 | 16 | 7 | - | 5 | - | 54 |
| Pagano, 2009 | Italy | 2004-2007 | 60 | 62 | 18 | 2 | - | 2 | 3 | 40 |
| Saegeman, 2010 | Belgium | 2000-2009 | 31 | 77 | 6 | 13 | - | 3 | - | 13 |
| Ruping, 2010 | Global | 2006-2009 | 41 | 63 | 17 | 10 | - | - | - | - |
| Skiada, 2011 | Europe | 2005-2007 | 230 | 55 | 17 | 9 | 1 | 2 | 7 | 20 |
| Chakrabarti, 2006 | India | 2001-2005 | 178 | 1 | 74 | 1 | - | - | - | 19 |
| Chakrabarti, 2009 | India | 2006-2007 | 75 | 9 | 44 | 5 | - | 1 | 29 | 14 |
| Lanternier, 2012 | France | 2005-2007 | 101 | 50 | 23 | 3 | - | - | - | 18 |

HM= Hematological malignancy, DM=Diabetes mellitus, DFO= Deferroxamine therapy, HIV= human immuno-deficiency virus, AI/CO= Autoimmune/corticosteroid therapy, SOM/SOT=Solid organ malignancy/transplant

# Risk factors in mucormycosis

| Reference | Count-ries | Period | Cases No. | HM (%) | DM (%) | SOM/ SOT | DFO (%) | HIV (%) | AI/ CO | Trauma/ no |
|---|---|---|---|---|---|---|---|---|---|---|
| Roden, 2005 | Global | 1885-2004 | 929 | 21 | 36 | 7 | 6 | 2 | 1 | 19 |
| Bitar, 2009 | France | 1997-2006 | 63 | 17 | 16 | 7 | - | 5 | - | 54 |
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| Chakrabarti, 2006 | India | 2001-2005 | 178 | 1 | 74 | 1 | - | - | - | 19 |
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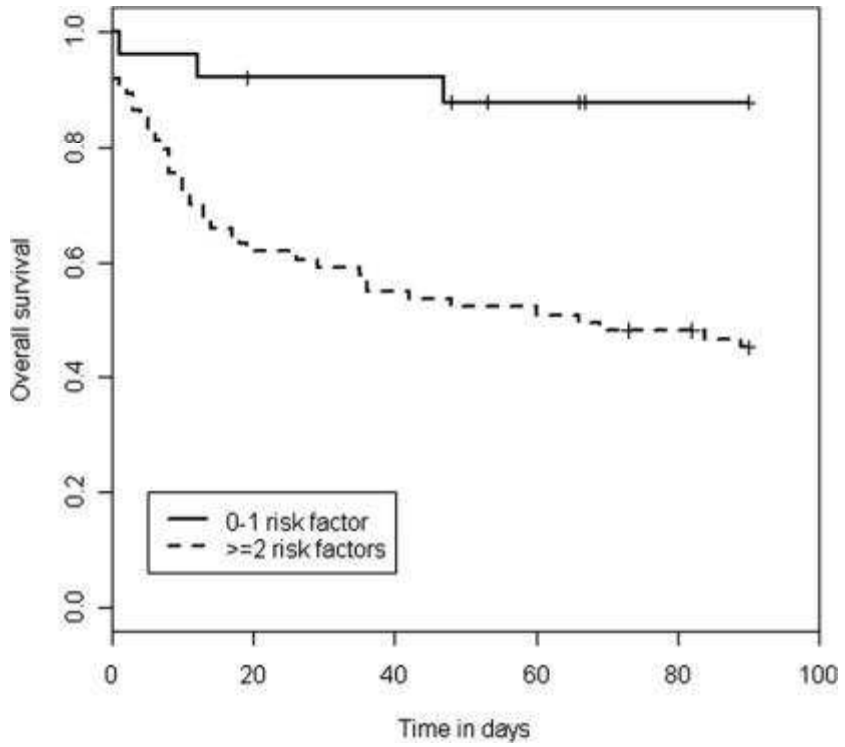
HM= Hematological malignancy, DM=Diabetes mellitus, DFO= Deferroxamine therapy, HIV= human immuno-deficiency virus, AI/CO= Autoimmune/corticosteroid therapy, SOM/SOT=Solid organ malignancy/transplant

# Multiple risk factors in haematological malignancy

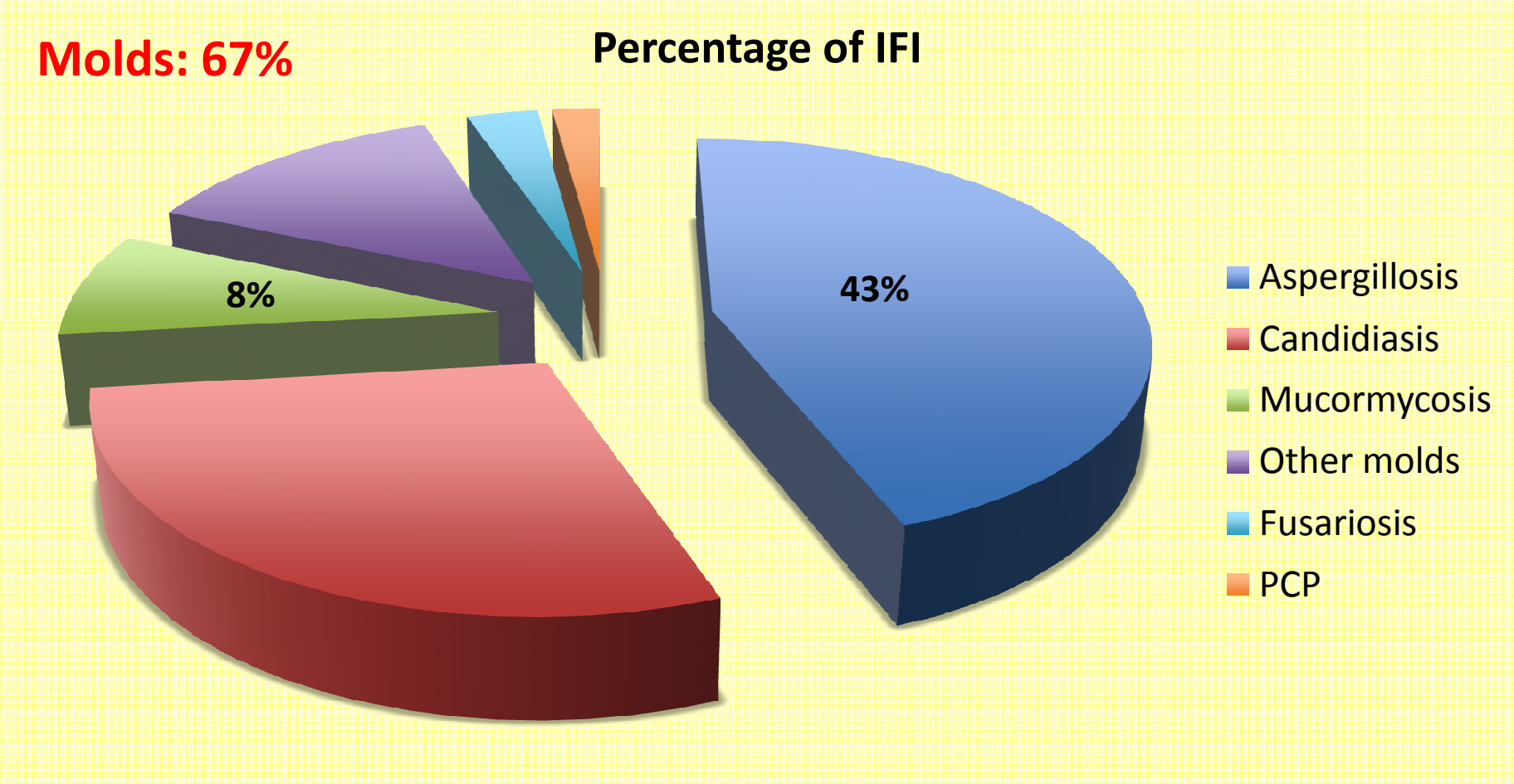
| Haematological malignancy | (50 patients) % |
|---|---|
| +HSCT | 24 |
| +GVHD | 10 |
| +Diabetes mellitus | 18 |
| +Corticosteroids | 26 |
| +Neutropenia | 80 |

**90-day survival vs. no. of risk factors**




Lanternier F *et al.* Clin Infect Dis 2012; 54: S35-S43

# Distribution of IFI in HSCT recipients




Kontoyiannis CID 2010

# Mucormycosis in Organ and Stem Cell Transplant Recipients

**Fanny Lanternier,[1,2,3] Hsin-Yun Sun,[5,6,7] Patricia Ribaud,[8,9] Nina Singh,[5] Dimitrios P. Kontoyiannis,[10] and Olivier Lortholary[1,2,3,4]**

**Clinical Infectious Diseases**

**Table 1. Studies Reporting >10 Cases of Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Recipients Who Received a Diagnosis of Mucormycosis**

| Study | Type of Study | No. of Patients/ Study Period | Outcome |
|---|---|---|---|
| Marr, single institution 2002 [23] | Retrospective | 29/1985–1999 | Median survival: 66 day<br>1-year survival rate: 20% |
| Roden, literature review 2005 [4] | Retrospective | 44/1940–2003 | Mortality rate: 91% |
| Kontoyiannis, single institution 2005 [24] | Prospective | 13/2002–2004 | Unreported for specific subpopulations |
| Trifilio, multicentric case series 2007 [25] | Retrospective | 34/2002–2005 | Mortality rate: 64% |
| Chamilos, single institution 2008 [5] | Retrospective | 32/1989–2006 | Mortality rate: 56% |
| Bitar, national hospital discharge codes 2009 [7] | Retrospective | 33[a]/1997–2006 | Mortality rate: 36.4% |
| Neofytos, active surveillance 2009 [26] | Prospective | 12/2004–2007 | 12-week mortality rate: 64.3%[b] |
| Kontoyiannis, active surveillance 2010 [6] | Prospective | 77[a]/2001–2006 | 1-year overall survival rate: 28% |
| Rüping, passive surveillance 2010 [20] | Prospective | 12/2006–2009 | Mortality rate: 75% |
| Skiada, passive surveillance 2011 [1] | Prospective | 21/2005–2007 | Mortality rate: 76% |

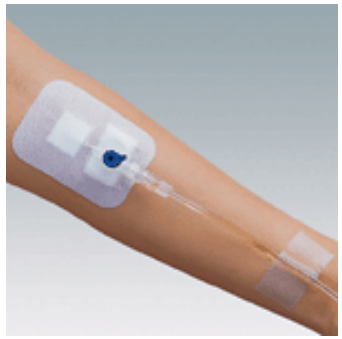
# Risk factors for mucormycosis in SOT

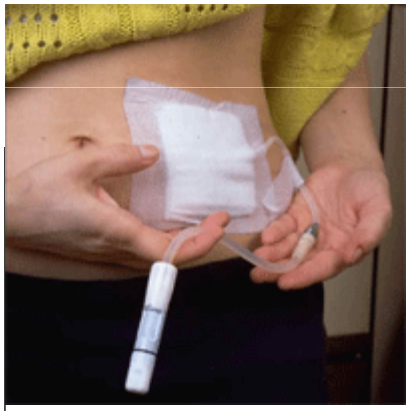
(Prospective cohort, 50 pts with paired control, multivariate analysis)

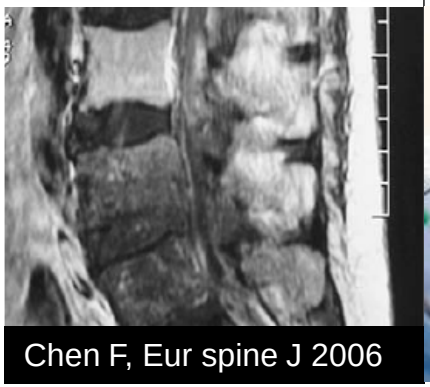
| Variables | OR (95% CI) | *P* |
|---|---|---|
| Re-transplant | 5.67 (0.86-37.5) | 0.072 |
| **Diabetes mellitus** | **8.11 (2.70-27.4)** | **<0.001** |
| Prior rejection | 2.62 (0.79-8.71) | 0.115 |
| **Renal failure at baseline** | **3.17 (1.31-7.65)** | **0.010** |
| **Prior voriconazole/ caspofungin** | **4.41 (1.12-17.3)** | **0.033** |
| **Tacrolimus immunosuppression** | **0.23 (0.09-0.57)** | **0.002** |

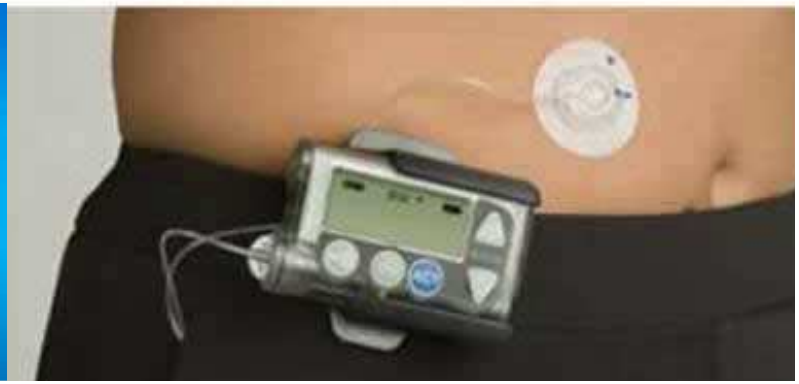
Singh N *et al*. JID 2009; 200: 1002-1011

# Medical devices as a source of nosocomial mucormycosis (Rammaert, CID 2012)




Chen F, Eur spine J 2006



# Published outbreaks of healthcare-associated mucormycosis

Rammaert et al. CID 2012

| Number of cases | Origin of contamination | Microorganism | Localization | Underlying condition | Death attributable to zygomycosis |
|---|---|---|---|---|---|
| 17 | Elastoplast | *R. microsporus* (n=8/17) | Skin | Surgery, steroids, cancer, diabetes mellitus | ? |
| 5 | Elastoplast | *L. corymbifer* | Skin | Burn unit | 3 (60%) |
| 5 | Wooden tongue depressors | *R. microsporus* | Digestive tract | ICU, steroids | 3 (60%) |
| 4 | Wooden tongue depressors | *R. microsporus* | Skin | Premature infant, steroids, hyperglycemia | 2 (50%) |
| 2 | Building construction | *M. indicus* (n=1/2) | Lungs | Premature infant | 2 (100%) |
| 3 | Building construction | *C. bertholletiae* | Lungs | Hematological malignancies | 2 (66%) |
| 2 | Ostomy bags | *Rhizopus sp.* | Skin | Surgery, steroids | 1 (50%) |
| 2 | Water circuitry damage | *R. pusillus* (n=1/2) | Rhinocerebral, disseminated | Hematological malignancies | 0/2 |

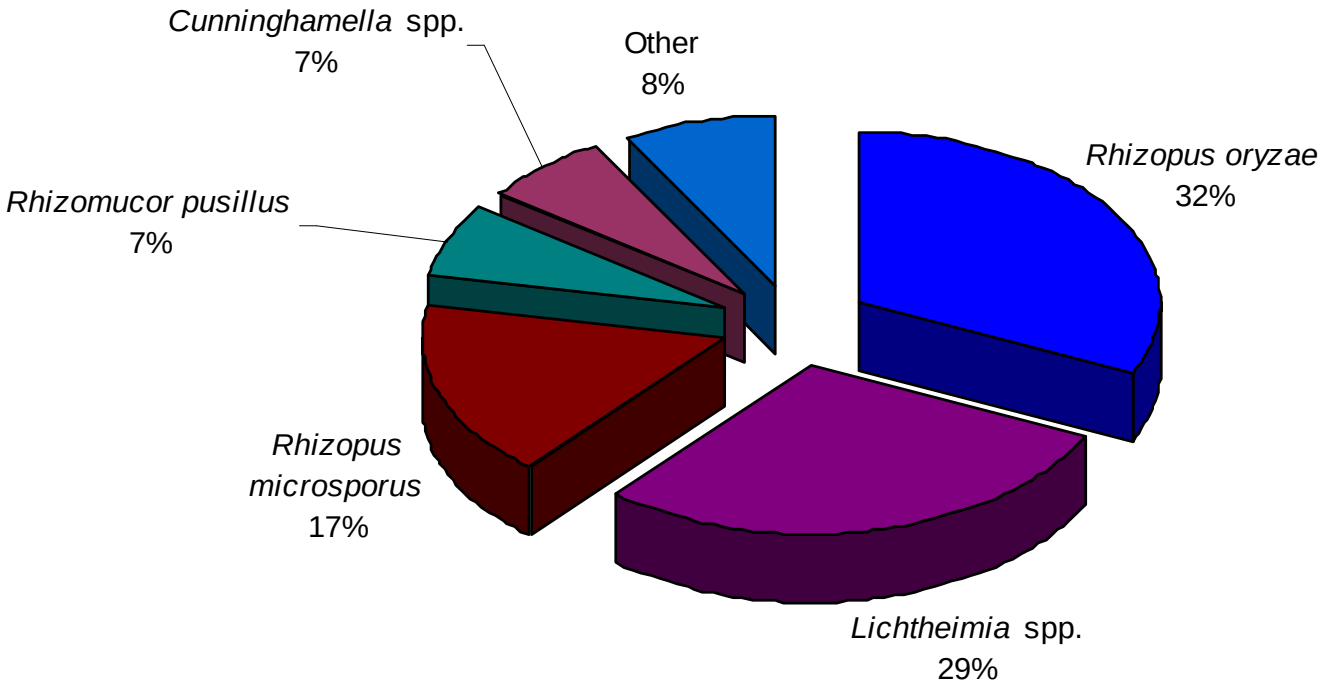
# Risk factors and clinical localization

| Predisposing conditions | Pathogenetic Mechanism | Clinical Presentation |
|---|---|---|
| **Haematological malignancy and HSCT** | Prolonged neutropenia | **Pulmonary and Sinus** > Cutaneous > Sino-orbital |
| Uncontrolled **diabetes mellitus** (metabolic acidosis) | Impaired neutrophil activation, interference in Fe binding to transferrin, ↑Fe usage by Mucorales | **Rhinocerebral** > Pulmonary > Sino-orbital > Cutaneous |
| Prolonged **corticosteroids**, Autoimmune disease | Defects in macrophages and neutrophils, Corticosteroid induced diabetes, Hypocomplementemia | **Disseminated > Renal >** Cutaneous > Rhinocerebral > Gastrointestinal Tract |
| **SOT and GVHD** | Cellular Immune suppression, Corticosteroid induced diabetes | **Pulmonary > Sinus >** Cutaneous > Rhinocerebral >Disseminated |
| **Intravenous drug abuse** | Injection of spores contained in drugs | **Cerebral > Cutaneous >** Renal > Heart > Rhinocerebral > Disseminated |

Petrikkos G *et al.* CID 2012; 54 (Suppl 1): S23-34

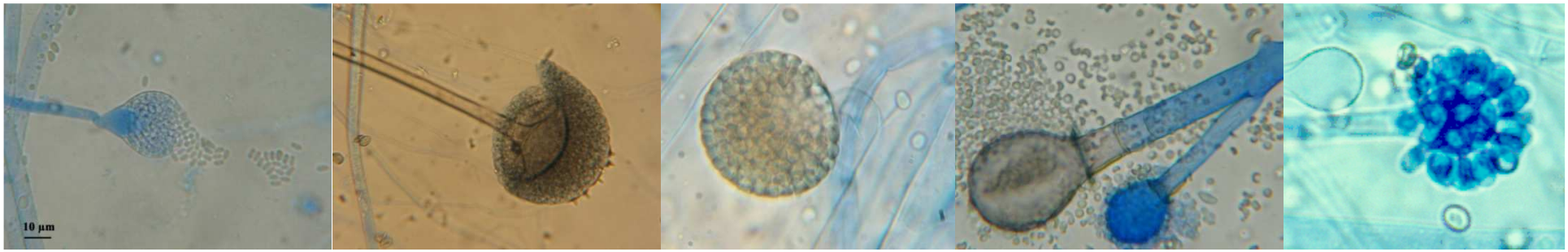
# Distribution of fungal species during mucormycosis in France

- « Retrozygo study», 101 mucormycosis cases 2005-2007




- ✓ *Rhizopus oryzae*: 85% of rhinocerebral forms vs 17% of non-rhinocerebral
- ✓ *Lichtheimia* spp. most frequent pathogen in diabetic patients

Lanternier F, CID 2012




# Treatment of mucormycosis

- General principles of mucormycosis therapy
- Role of aggressive surgery (rhino-oculo-cerebral)
- Antifungal therapy
  - *In vitro* data
  - Contribution of experimental therapeutics
  - Clinical data
- ECIL3 guidelines proposal

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# General therapeutic principles

## 1. Control host factors

Taper steroids

Hold immunosuppressive moAb (anti-TNF-α, alemtuzumab)

Control hyperglycemia (Rammaert, Diabetes Metabolism 2012)

## 2. Early appropriate antifungal therapy

## 3. Surgery

Any localisation when feasible, but rhino-oculo-cerebral +++

Extent and timing of debridment remains unknown

Delineate margins of infected tissues (Reed C *et al.* CID 2008; 47: 364-371)

Independent factor of decreased mortality (Roden M *et al*, CID 2005; 41: 634-653)

Subsequent reconstructive surgery

# Early amphotericin B based therapy

(70 haematology pts, 1989-2006)

- **Mortality**:
  - Early therapy (<7d after first symptoms): 35%
  - Delayed: 67%

- Multivariate analysis of factors associated with survival:
  - **Early therapy**
  - Lack of evolutive malignancy
  - Neutrophil recovery
  - Salvage therapy with PCZ

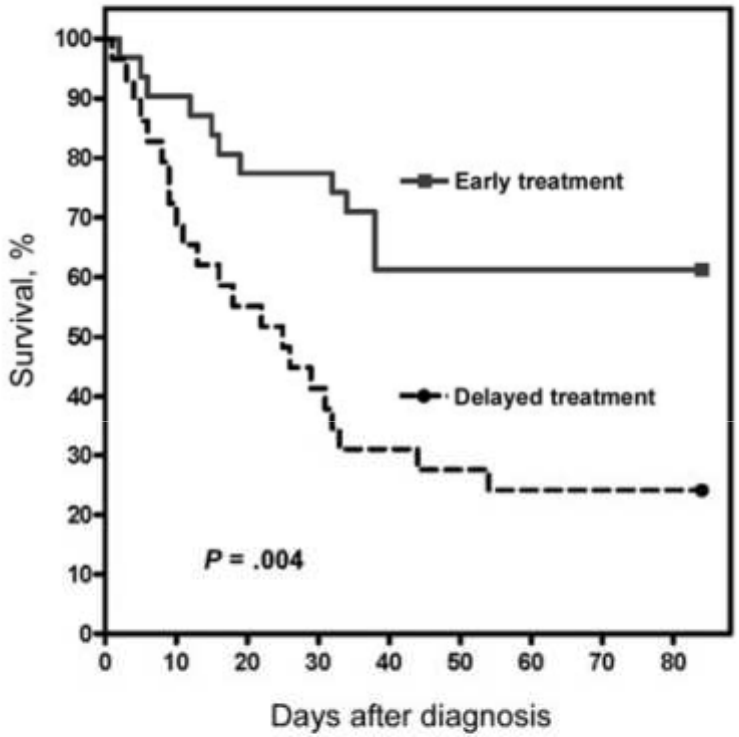



**Figure 4.** Kaplan-Meier probability of survival after the diagnosis o zygomycosis, according to the timing of initiation of amphotericin B–based treatment ($P = .004$, by log-rank test). Early treatment was define as receipt of effective amphotericin B–based treatment <6 days afte diagnosis, and delayed treatment was defined as receipt of effective amphotericin B–based treatment ≥6 days after diagnosis.

Chamilos G *et al*. CID 2008; 47; 503-509

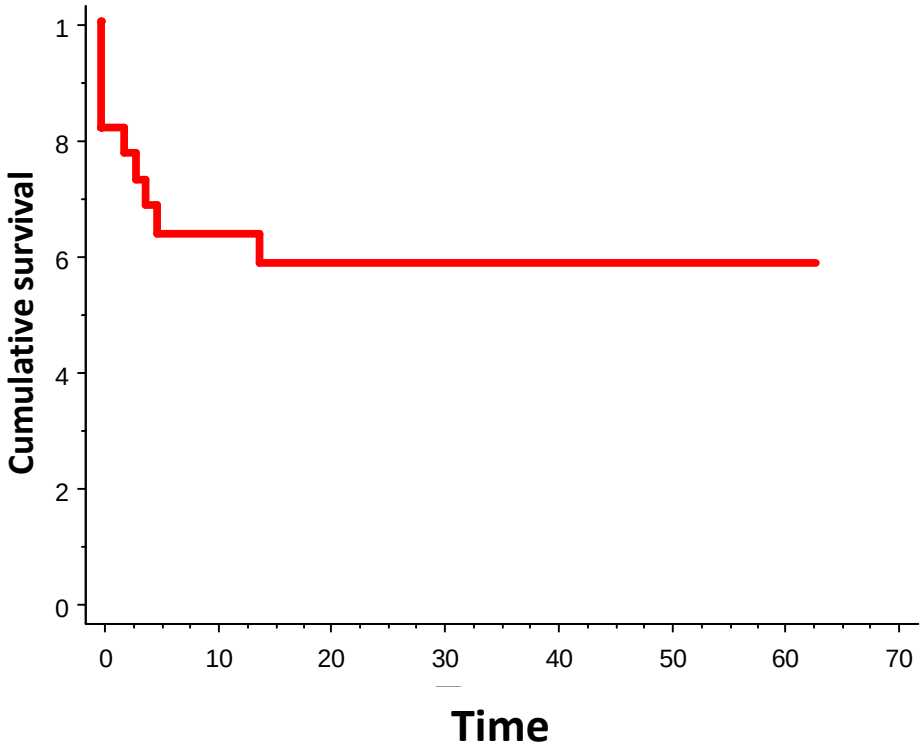
# ROLE OF AGGRESSIVE SURGERY

# Survival in rhinocerebral mucormycosis

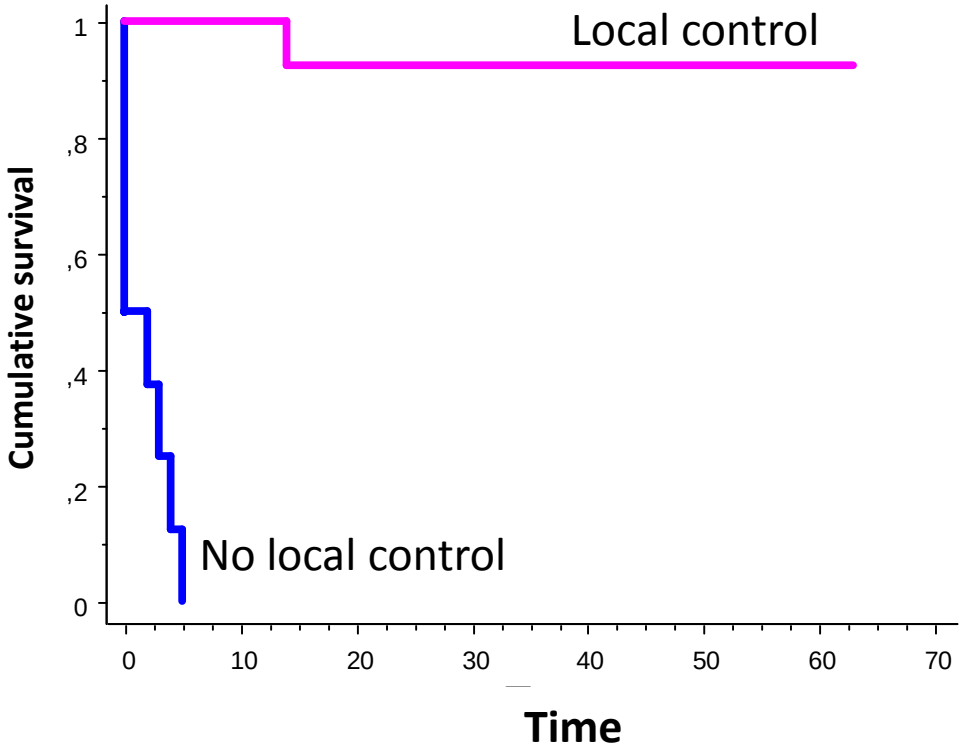
(From Retrozygo Study; Lanternier et al. CID 2012; n=22)

## Actuarial survival estimate

*(Overall survival rate 57%)*

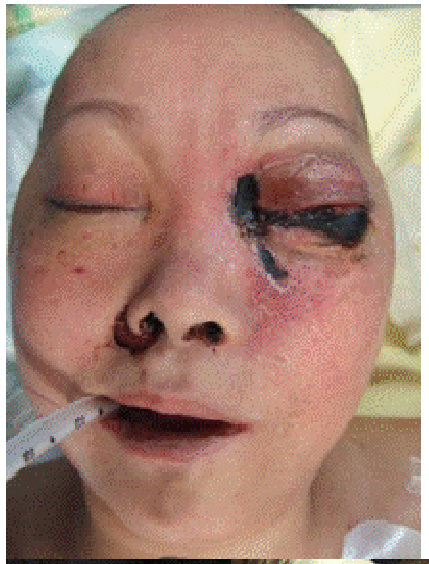


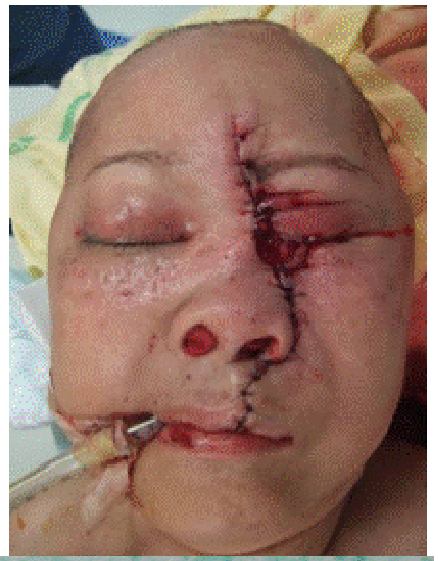

## Actuarial survival estimate

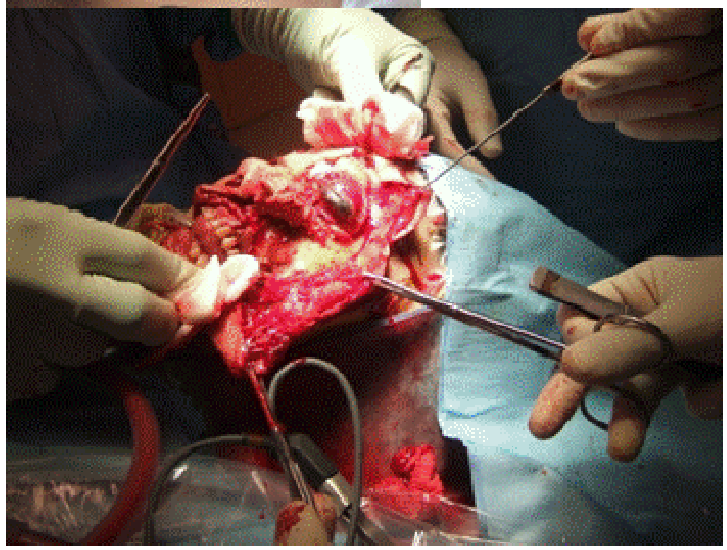


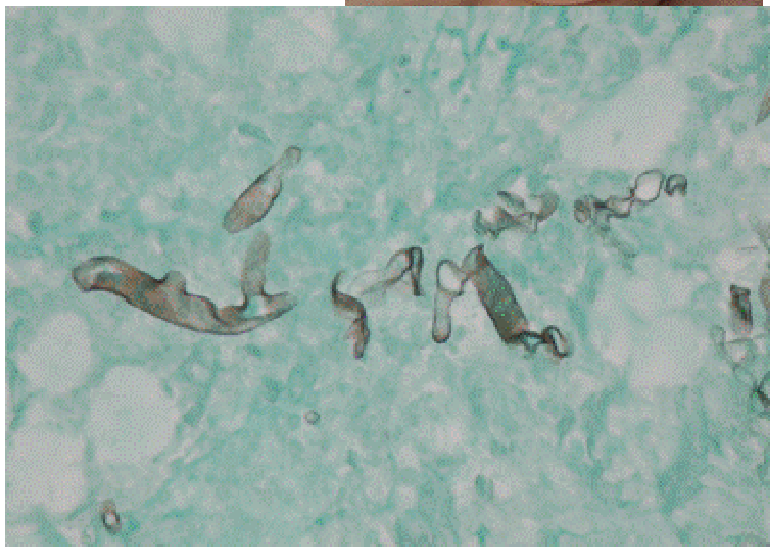

Vironneau *et al ICAAC 2012*

# Radical surgery during rhino-oculo-cerebral mucormycosis









# ANTIFUNGAL THERAPY

*In vitro* data

Contribution of experimental therapeutics

Human data

- Polyenes (lipid formulations of AmB)
- Posaconazole
- Combination therapy

# *In vitro* data

## (n=217 Mucorales isolates)

| | Amphotericin B % with MIC ≤1µg/mL | posaconazole % with MIC ≤0.5µg/mL | itraconazole % with MIC ≤0.5µg/mL |
|---|---|---|---|
| ***Rhizopus*sp** ***(101)*** | 100 | 80 | 62 |
| ***Rhizopus arrhizus (20)*** | 100 | 64 | 50 |
| ***Rhizopus microsporus (12)*** | 100 | 78 | 60 |
| ***Mucor* sp. *(41)*** | 94 | 70 | 57 |
| ***Mucor circinelloides (6)*** | 100 | 0 | 0 |
| ***Rhizomucor* sp *(5)*** | 100 | 67 | 67 |
| ***Lichtheimia* sp. (3)** | 100 | 100 | 50 |
| ***Lichtheimia corymbifera (9)*** | 100 | 100 | 100 |
| ***Cunninghamella* sp. *(13)*** | 63 | 75 | 29 |
| ***Apophysomyces elegans (6)*** | 100 | 83 | 80 |

Almyroudis NG *et al*. AAC 2007; 51; 2587-2590

# Liposomal amphotericin B for primary mucormycosis therapy

- Retrospective study (5 centres): 1998 - 2005
- 46% haematological malignancies, 50% pulmonary localisation
- 46% surgery

**Table 4** Treatment administered to 28 patients with zygomycosis who received primary L-AMB therapy.

| Treatment | Number (%) of all patients | Number (%) of all patien with a successful response[a] | Number of patients who survived/ total number who received treatment (%) |
|---|---|---|---|
| L-AMB for primary therapy | 28 (100) | 9/28 (32) | 11/28 (39) |
| Concomitant surgery | 13 (46) | 4/13 (31) | 4/13(31) |
| Concomitant immunomodulation | | | |
| Overall | 10 (36) | 2/10 (20) | 3/10 (30) |
| GCSF | 7 (25) | 2/7 (29) | 3/7 (43) |
| GM-CSF | 1 (4) | 0/1 (0) | 0/1 (0) |
| Granulocyte transfusions | 2 (7) | 0/1 (0) | 0/2 (0) |

[a] Successful response is defined as complete or partial global response at end of L-AMB therapy.

Shoam, Med Mycol 2010

# Posaconazole for human mucormycosis

- Retrospective study of mucormycosis (n=91) refractory or with intolerance to a reference therapy
- 52% haematological malignancy, 30% allo-SCT
- Posaconazole: 800 mg/d (duration according to response and persistance of immune deficiency)
- W12 response: 60% (Complete:14%, Partial:46%)
- W12 survival: 62%

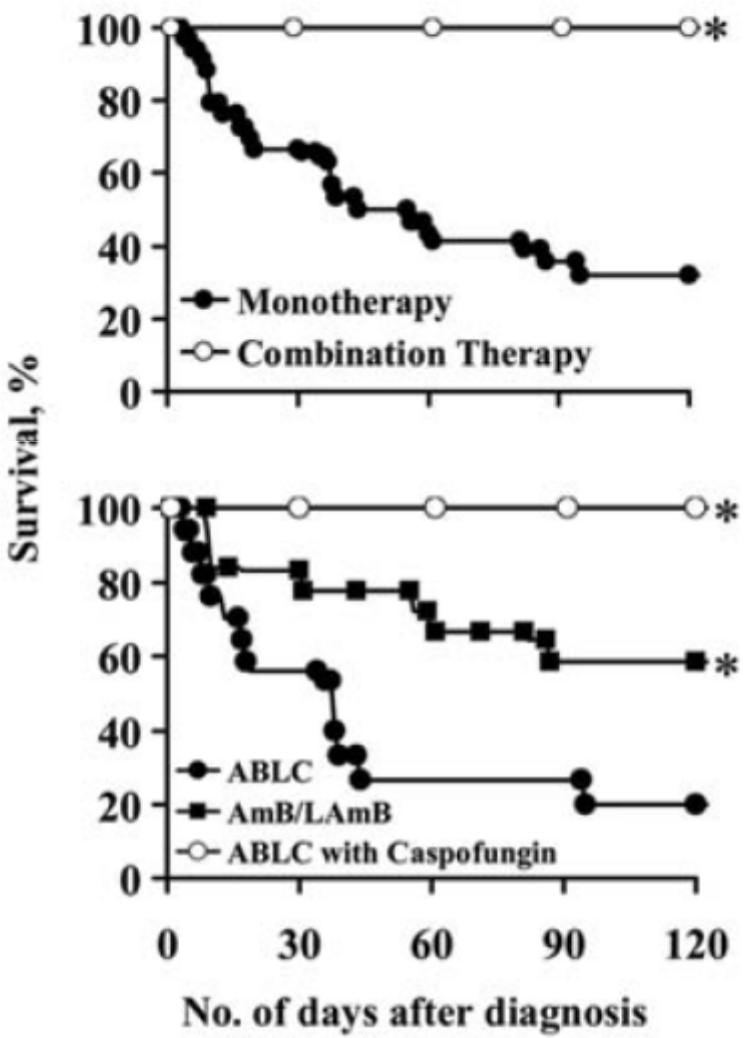
***But monitoring is needed after 7d of therapy; serum concentration ≥ 1 μg/ml***

***Check: compliance; suboptimal absorption; drug-drug interaction***

Van Burik J *et al.* CID 2006; 42: e61-5

# Combination of polyenes and caspofungin:
## 30d post hospitalisation survival data

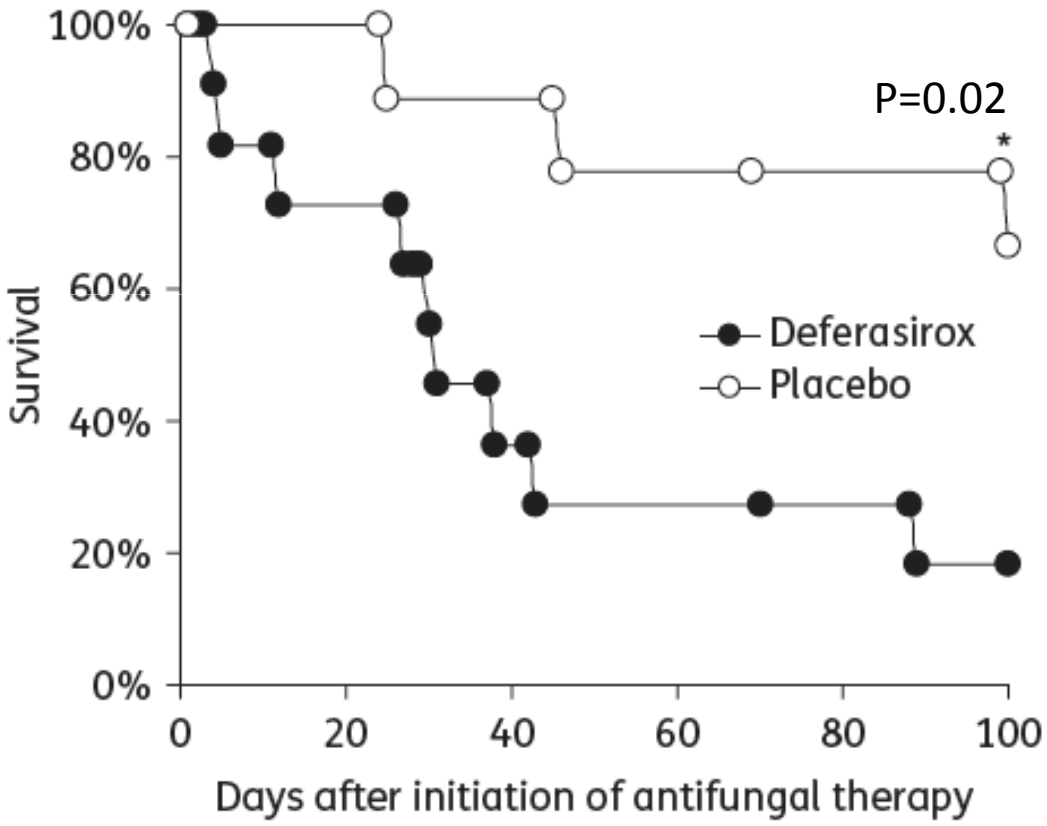
- Bicentric retrospective study (1994-2006)
- Rhino-orbital-cerebral mucormycosis; 83% Db
- n=41 (7 combo)
  - AmB alone: n=15
  - ABLC (5 mg/kg/d): n=22, of which 5 + CAS
  - LAmB (5 mg/kg/d): n=4, of which 2 + CAS
- Polyene alone: 45%
  - ABLC = 37%
  - LAmB = 72%
  - Combo = 100%




Reed C *et al.* CID 2008: 47: 364-371

# Defeat Study : LAmB ± Deferasirox

DB vs. placebo 14d; LAmB ≥ 5 mg/kg/tiw
Imbalances hemo/onc/pulm infections




Comparable safety

Spellberg B *et al.* JAC 2012; 67: 715-722

# AMBIZYGO Trial (France)

Pilot prospective study of high dose liposomal amphotericin B for the initial treatment of mucormycosis (n=40)

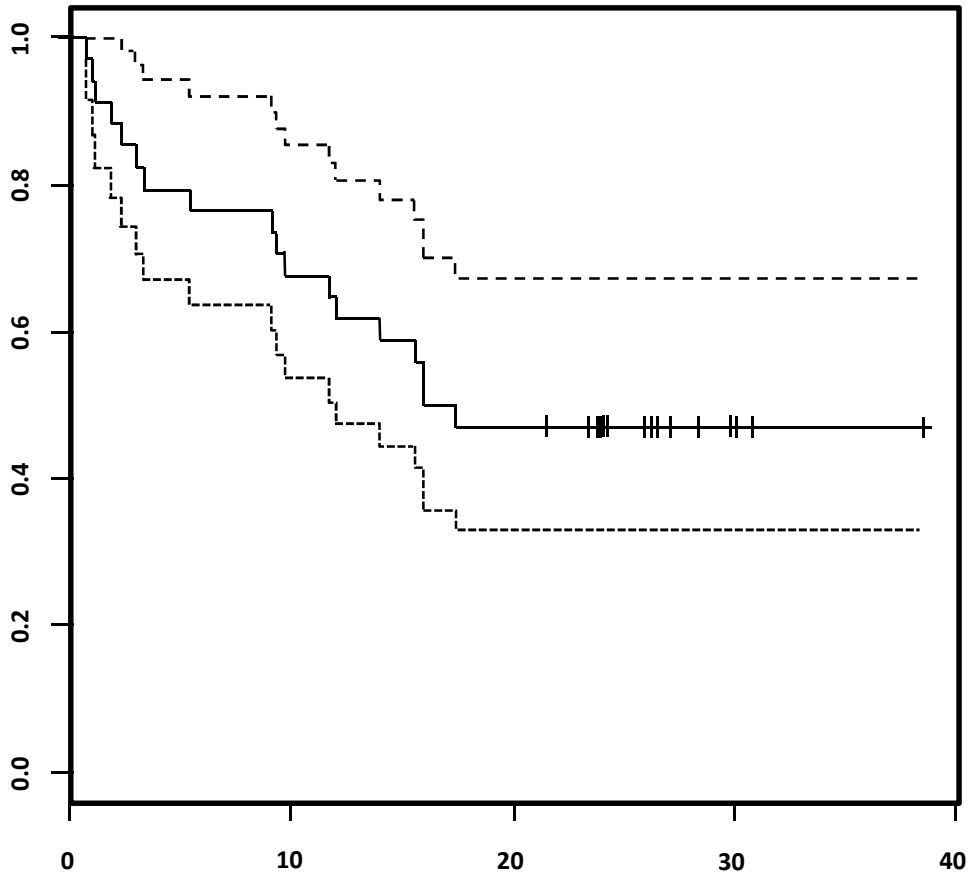
10 mg/kg/d LAmB or maximal tolerated dose for one month

53% haematological malignancy

Proven or probable cases

| | N (%) |
|---|---|
| **Success** | **14 (45.2%)** |
| Complete | 10 |
| Partial | 4 |
| Failure | **17** |
| Stable | 2 |
| Failure | 2 |
| Death | 13 |

**Response at week 12**




**Survival: 47% [33-67] at M6**

Lanternier *et al*. ICAAC 2012

# Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3)

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# ECIL3 recommendations:
## 1st line therapy

| | |
|---|---|
| Management should include antifungal therapy, control of underlying conditions and surgery | **A II** |
| **Antifungal therapy** | |
| AmB deoxycholate | **C II** |
| Liposomal AmB $\geq$ 5 mg/kg/d | **B II** |
| ABLC | **B II** |
| ABCD | **C II** |
| Posaconazole | **C III** |
| Combination therapy | **C III** |
| Control of underlying condition | **A II** |
| **Surgery** | |
| Rhino-orbito-cerebral | **A II** |
| Soft tissue | **A II** |
| Localised pulmonary lesion | **B II** |
| Disseminated | **C III** |

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# ECIL3 recommendations:
## 2nd line and maintenance therapy

| | |
|---|---|
| Posaconazole | **B II** |
| Combination lipid AmB and caspofungin | **B II** |
| Combination lipid AmB and posaconazole | **C III** |
| Combination with deferasirox | **C III** |

**Maintenance therapy**

| | |
|---|---|
| Posaconazole | **B III** |

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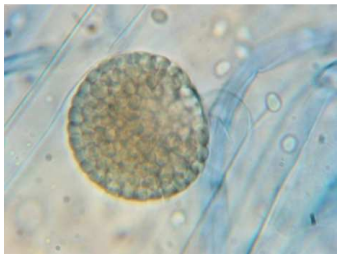
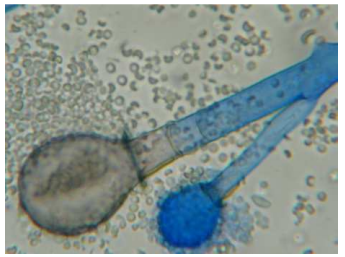
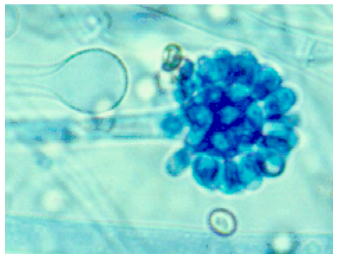

# Conclusion

- Increased clinical and microbiological awareness as epidemiology is moving !
- Mucormycosis should be differentiated from other filamentous fungal infections
- Management in specialized centres
  - Control of underlying disorders
  - Aggressive surgery (rhino-orbital-cerebral) with 2nd look? [PHRC MICCA]
  - Early administration of a lipid formulation of AmB (LAmB if brain)
  - Rationale for high dose LAmB
  - No role for iron chelation (in haematology patients)
  - Towards new clinical trials