



Infections fongiques et transplantation d'organe: à propos de deux situations cliniques

Olivier Lortholary

Centre d'Infectiologie Necker-Pasteur

Université Paris Descartes, Hôpital Necker Enfants malades,
IHU Imagine &

Centre National de Référence Mycologie & Antifongiques,
Unité de Mycologie Moléculaire, CNRS URA3012
Institut Pasteur, Paris, France.

**First clinical case: severe sepsis in a
recently kidney transplanted
69-years-old woman**

Medical history

Caen

- Chronic renal failure/nephroangiosclerosis 1993
- Dialysis started April 2007
- Kidney transplantation 27th December 2007
 - Steroids/ciclosporin and mycophenolate mofetil
- Severe sepsis due to *E. coli* 28th January 2008
- Serum creatinin level : 141 $\mu\text{Mol/l}$

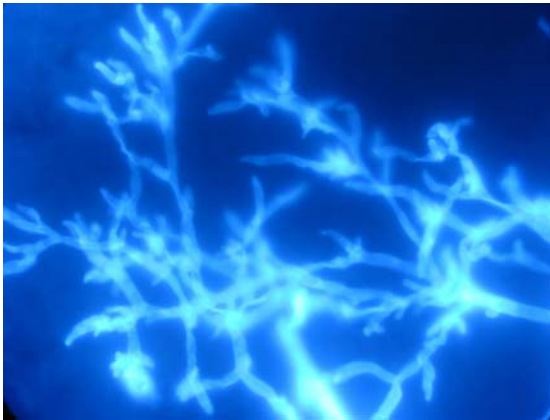
End of February 2008

(2 months post grafting)

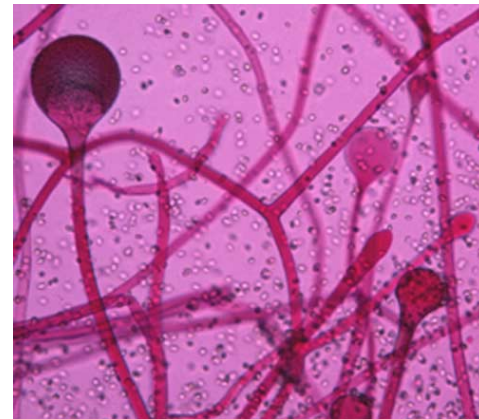
- New severe sepsis
- Acute renal failure
- Liver enzyme changes
- CMV reactivation
- Multiple skin lesions



Question 1: what is your diagnosis?



Microscopic examination
of skin/liver/grafted
kidney samples



Positive cultures: skin,
BAL, renal graft

**Disseminated mucormycosis due to
Lichtheimia (Absidia) corymbifera
with skin, pulmonary, liver and
kidney graft involvement**

Question 2: Does the incidence of mucormycosis increase and what is the percentage of mucormycosis among IFI in SOT recipients?

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

Emerg Infect Dis Sept 09

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

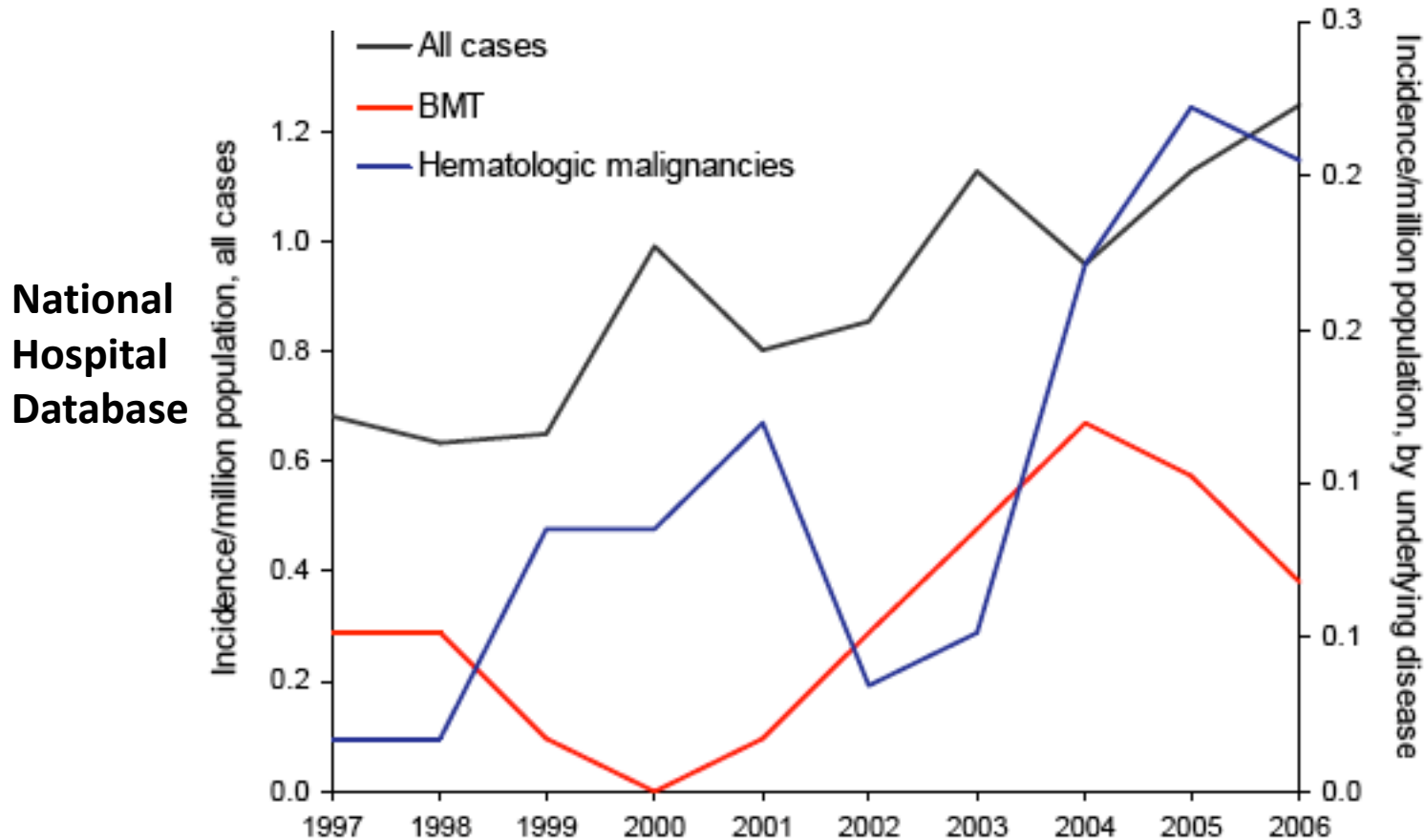


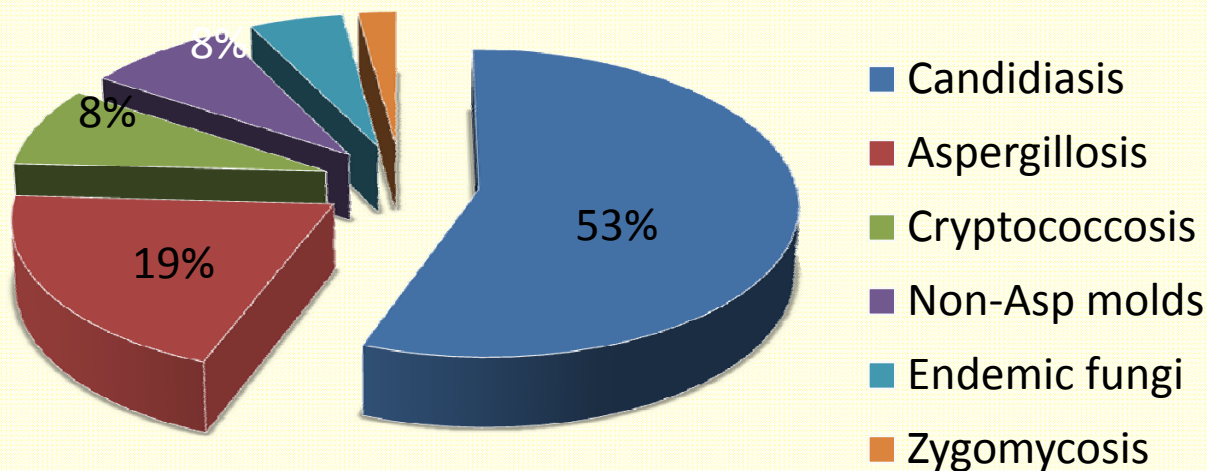
Figure 1. Evolution of the incidence of zygomycosis, France, 1997–2006. BMT, bone marrow transplantation.



Distribution of IFI in SOT recipients:

TRANSNET data

1208 IFI in 1063 organ transplant recipients



Mucormycosis : 2% of IFI in SOT recipients

Pappas, CID 2010

IFI by transplant type

IFI type	Kidney (n = 332)	Liver (n = 378)	Pancreas (n = 128)	Lung (n = 248)	Heart (n = 99)	Small bowel (n = 22)
Candidiasis	164 (49)	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)

3. What are the risk factors of SOT-associated mucormycosis?

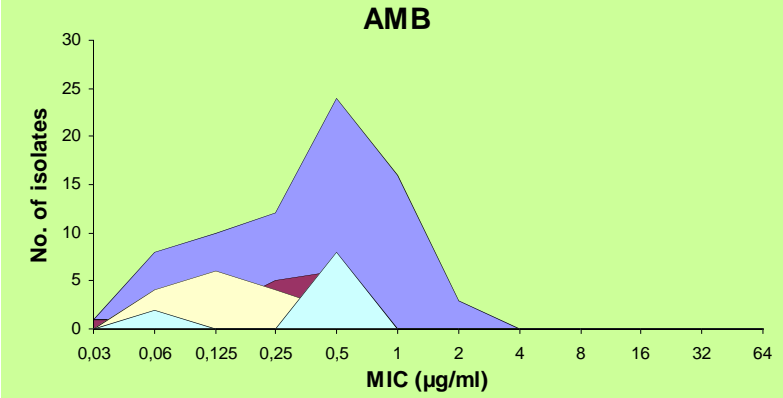
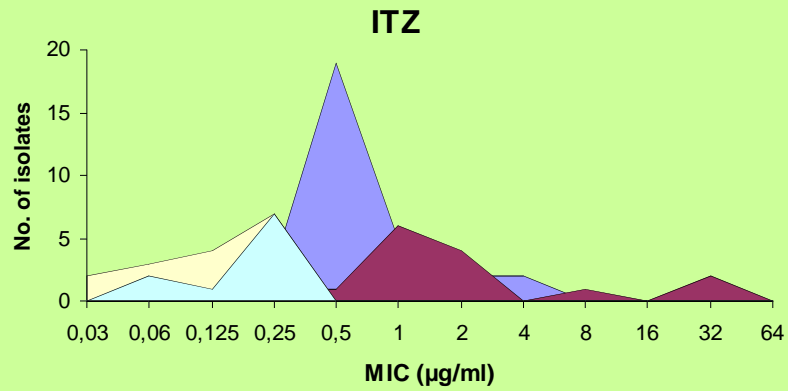
Risk factors of IFI in SOT: aspergillosis and mucormycosis

- **Aspergillosis:** retrospective case-control study (OR)
 - ≤ 3 months =
 - Difficult post-operative period (2.9)
 - CMV disease (2.3) & bacterial inf (3.2)
 - Renal failure (4.9)
 - > 3 months =
 - Age > 50 yrs (2.5)
 - Immunosuppress related neoplasia (69.3)
 - Chronic rejection (5)
 - Renal failure (3.9)
- **Mucormycosis:** prospective international matched case-control study (OR)
 - *higher risk* =
 - Renal failure (3.17)
 - Diabetes mellitus (8.11)
 - Prior voriconazole and/or caspofungin use (4.41)
 - *lower risk* =
 - Tacrolimus (0.23)

4. What is the treatment of SOT-associated mucormycosis?

Zygomycetes : distribution of antifungal MICs

**NRCMA,
Inst Pasteur**

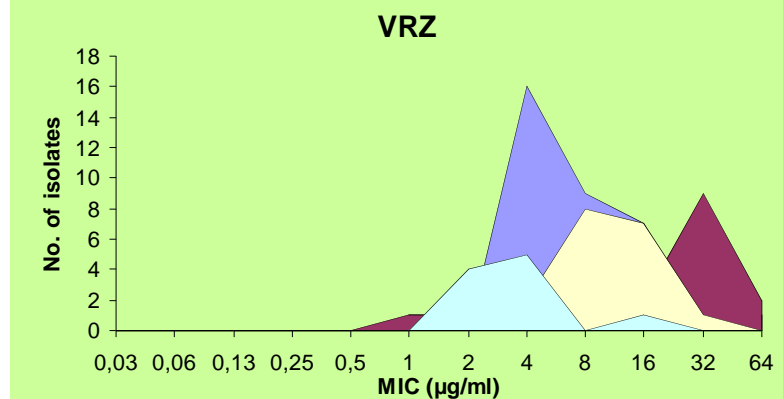
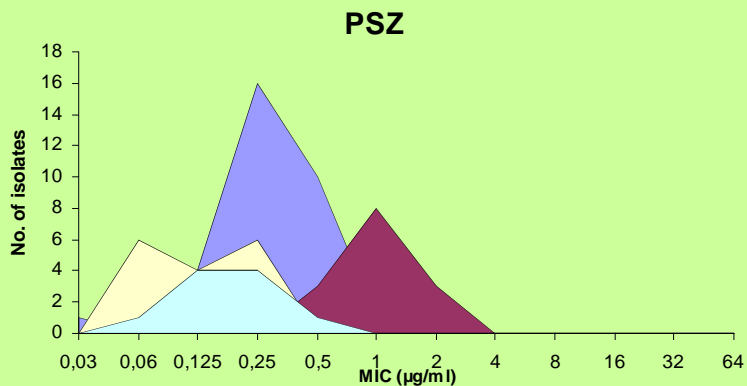


■ *Absidia* spp.

■ *Mucor* spp.

■ *Rhizopus* spp.

■ *Rhizomucor* spp.



Treatment of SOT-associated mucormycosis

- Success with liposomal AmB 4-fold higher
- A lipid formulation of amphotericin B is the recommended first line therapy [ECIL 3, 2009]
- Surgical resection = higher success (OR 33.3, p=0.003)
Singh et al. JID 2009
- Discontinuation or reduction of immunosuppression = better survival rate *Almyroudis AJT 2006*

Thank you!!!



Rencontres nationales :
Actualités sur les

Mucormycoses

Le Comité scientifique

sous la présidence du **Pr Olivier Lortholary, Hôpital Necker, Paris**

Dr Dounia Bitar (Unité des Maladies Infectieuses,
Institut National de Veille Sanitaire, Saint Maurice)

Pr Raoul Herbrecht (Hôpital Hautepierre, Strasbourg)

Dr Dea Garcia Hermoso-Kaiser (Centre National de Référence Mycologie
et Antifongiques, Institut Pasteur)

Dr Romain Kania (Hôpital Lariboisière, Paris)

Dr Fanny Lanternier (Hôpital Necker, Paris)

Programme

vendredi 24 juin 2011
de 13h à 17h

12h00 Accueil - Cocktail déjeunatoire

13h00 Introduction du président de séance, Olivier Lortholary

13h10-13h40 Conférence par le Dr Patrice Josset, historien
de la médecine : "La découverte des mucormycoses"

13h40-15h00 Epidémiologie et clinique des mucormycoses

- Epidémiologie : Dounia Bitar (15')
- Diagnostic clinique : Raoul Herbrecht (25')
- Diagnostic microbiologique : Dea Garcia Hermoso (20')
- Table ronde (20')

15h00-15h20 Pause

15h20-16h40 Prise en charge médico-chirurgicale des mucormycoses

- Stratégie antifongique : Fanny Lanternier (30')
- Le point de vue du chirurgien ORL : Romain Kania (30' dont film 10')
- Table ronde (20')

16h40-17h00 Conclusion du président de séance, Olivier Lortholary

**Second clinical case: sepsis in a
kidney transplanted
55-years-old African man**

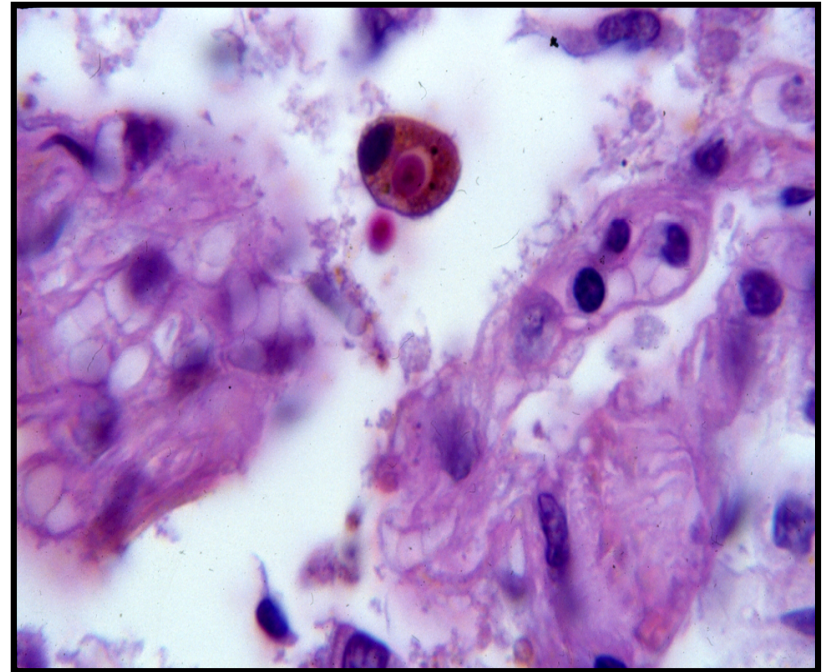
Medical history

- Chronic renal failure/nephroangiosclerosis 1998
- Dialysis started April 2003
- Kidney transplantation May 2005
 - Steroids/tacrolimus and mycophenolate mofetil
- Increased immunosuppression with ATG due to graft rejection 2007
- Admitted for sepsis (no CVC) + multiple skin nodules in November 2007
- Blood culture grew a yeast/urine culture negative

1st question: what is your diagnosis?

Disseminated cryptococcosis in a SOT pt

- 2125 cases in France (1985-2001)
- 1644 AIDS cases (77.4%)
- 335 HIV negative :
 - 17.4% SOT
 - 36.8% Hem malign/cancers
 - 20.4% various underlying dis
 - 25.4% no known immune deficit



2. What is the epidemiology of SOT-associated cryptococcosis ?

IFI by transplant type

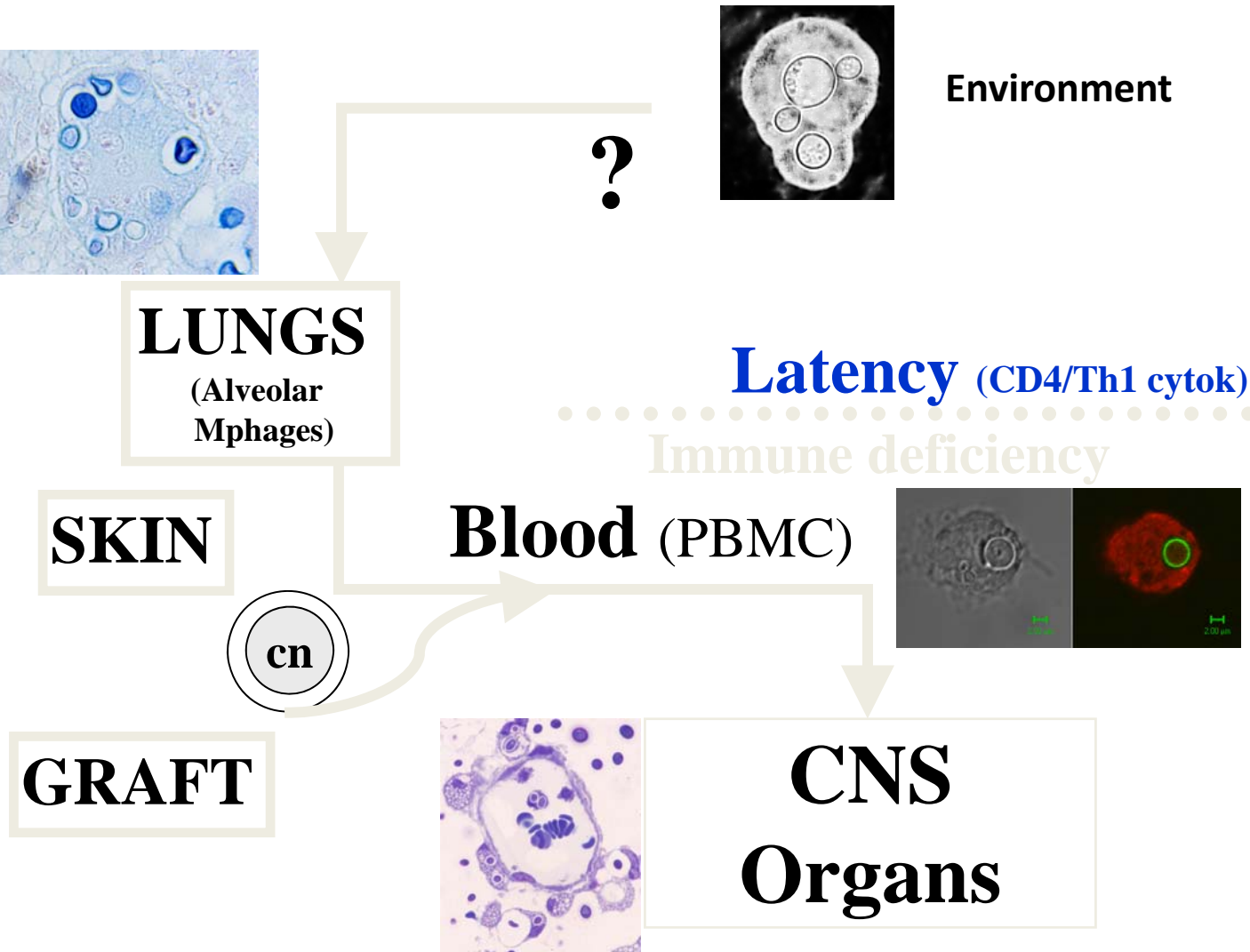
IFI type	Kidney (n = 332)	Liver (n = 378)	Pancreas (n = 128)	Lung (n = 248)	Heart (n = 99)	Small bowel (n = 22)
Candidiasis	164 (49)	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)

Epidemiology of SOT-associated cryptococcosis

- ✓ Prevalence : 0.26-5%; 70.1-78% male
- ✓ Major role of steroids [Husain Emerg Infect Dis 2001; Wu Transpl Infect Dis 2002; Vilchez Am J Transplant 2002; Jabbour Transplantation 1996; John Transplantation 1994]
- ✓ Incidence after anti-thymocyte Ig or alemtuzumab (anti CD-52) [Silveira, Transpl Infect Dis 2007] :
 - ✓ 0.26% (2/781) if not
 - ✓ 0.3% (2/646) after 1 dose
 - ✓ 2.24% (3/134) after 2 doses ($p = 0,03$)
 - ✓ Median time of occurrence 255 d (7-517 d), 14.2% mortality
- ✓ Alemtuzumab used for rejection [OR = 3.5; 95%CI, 1.8-6.8] [Peleg, CID 2007]

3. What is the pathogenesis of cryptococcosis in SOT recipients

C. neoformans infection pathogenesis during SOT



**R
E
P
R
I
M
A
R
Y
I
N
F
?**

**R
E
A
C
T
I
V
A
T
I
O
N
?**

4. What is the percentage of SOT recipients with cryptococcosis who have meningeal involvement?

Identifying Predictors of Central Nervous System Disease in Solid Organ Transplant Recipients With Cryptococcosis

Ryosuke Osawa,^{1,2} Barbara D. Alexander,³ Olivier Lortholary,^{4,5} Françoise Dromer,⁵ Graeme N. Forrest,⁶ G. Marshall Lyon,⁷ Jyoti Somani,⁷ Krishan L. Gupta,⁸ Ramon del Busto,⁹ Timothy L. Pruett,¹⁰ Costi D. Sifri,¹⁰ Ajit P. Limaye,¹¹ George T. John,¹² Goran B. Klimmalm,¹³ Kenneth Pursell,¹⁴ Valentina Seosor,¹⁵ Michele I. Morris,¹⁶ Lorraine A. Dowdy,¹⁶ Patricia Muñoz,¹⁷ Andre C. Kalil,¹⁸ Julia Garcia-Diaz,¹⁹ Susan Orloff,²⁰ Andrew A. House,²¹ Sally Houston,²² Dannah Wray,²³ Shirish Huprikar,²⁴ Leonard B. Johnson,²⁵ Atul Humar,²⁶ Raymond R. Razonable,²⁷ Robert A. Fisher,²⁸ Shahid Husain,²⁹ Marilyn M. Wagener,² and Nina Singh^{1,2,30}

(*Transplantation* 2010;89: 69–74)

- 129 (88%)/146 SOT recipients with cryptococcosis with CSF analysis
 - 80 (62%) had CNS disease
- Increased risk of CNS disease :
 - abnormal mental status,
 - > 24 months post-transplantation
 - CPS titer > 1:64
 - fungemia

**Lumbar
puncture
mandatory
for these
patients**

5. Is cryptococcal antigen always positive during cryptococcal meningitis in SOT recipients?

Cryptococcosis diagnosis: extensive work up

(Dromer et al. PLoS Medicine 2007)

Parameter	Percentage of patients (n) according to HIV status				P
	Positive (n = 177) ^a		Negative (n = 53)		
Mycological results					
Positive blood culture	46	(168)	12	(51)	< 10 ⁻³
Positive CSF culture	89	(176)	69	(42)	0.003
Positive urine culture	30.5	(154)	25	(52)	NS
Disseminated infection	61	(170)	39	(52)	0.007
Serotype A isolate	76	(171)	61	(51)	0.048
Positive serum antigen detection in tested patients w:	95	166	74.5	51	< 10 ⁻³
Disseminated cryptococcosis	100	(96)	89	(19)	0.028
Meningoencephalitis	97	(146)	86	(29)	0.027
Mean serum antigen titer in log2 [95%CI]	9.2 [8.5 – 9.9]	(158)	6.1 [4.9 – 7.3]	(38)	< 10 ⁻³
CSF characteristics in patients with meningoencephalitis^c					
Positive India ink	88	(156)	52	(31)	< 10 ⁻³
Median CSF cell count/mm ³ [IQR] ^d	9 [2 – 65]	(153)	31 [1 – 130]	(29)	NS
Median CSF protein conc (g/l) [IQR]	0.7 [0.4 – 1.2]	(152)	0.85 [0.5 – 1.1]	(31)	NS
Mean CSF:serum glucose conc. [95%CI]	0.46 [0.42 – 0.50]	(141)	0.35 [0.27 – 0.44]	(26)	0.040
Positive CSF antigen	97	(141)	100	(27)	NS
Mean CSF antigen titer (log2)[95% CI]	8.3 [7.6 – 9.0]	(137)	6.2 [4.3 – 8.1]	(29)	0.019

6. What is the first line therapeutic strategy during cryptococcal meningitis in SOT recipients?

Management of cryptococcal meningitis in SOT Patients

IDSA Guidelines CID 2010

Regimen	Duration	Evidence
Induction therapy: ^a liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day) ^b	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

^a Immunosuppressive management may require sequential or step-wise reductions.

^b Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction with calcineurin inhibitors are important and the effective dose is imprecise.

Flucytosine monitoring : 30-80 µg/ml 2h after administration

Are lipid formulations of AmB better for CNS cryptococcosis in SOT ?

Sun et al. CID 2009

75 patients with SOT-cryptococcosis treated with polyenes

- 55 (73.3%) received lipid formulations
- 20 (26.7%) received AmBd
- Overall mortality at 90 d
 - 10.9% w AmB lipid formulations
 - 40.0% w AmBd
- AmB lipid formulations independently associated with a lower mortality (OR, 0.11; 95% CI,0.02-0.57; P = .008)
- Mortality did not differ with or without flucytosine

7. What are the prognostic factors of cryptococcosis in SOT recipients?

Risk factors for death during SOT-associated cryptococcosis

A study of 111 patients

Singh et al. JID 2007

- ✓ Use of calcineurin inhibitors : HR = 0.21, p = 0.008
- ✓ Renal failure : HR = 3.14, p = 0.037 [only factor found in literature review Husain EID 2001]
- ✓ 14% mortality rate at day 90 (42% in literature review; Husain EID 2001)
- ✓ During meningitis : vigilance disturbances, lack of headache and liver failure [Wu, Transpl Infect Dis 2002]

Journée GTI en Mars

olivier.lortholary@nck.aphp.fr



DIU INFECTION TRANSPLANTATION

Organisé par GTI

emmanuel.morelon@chu-lyon.fr