

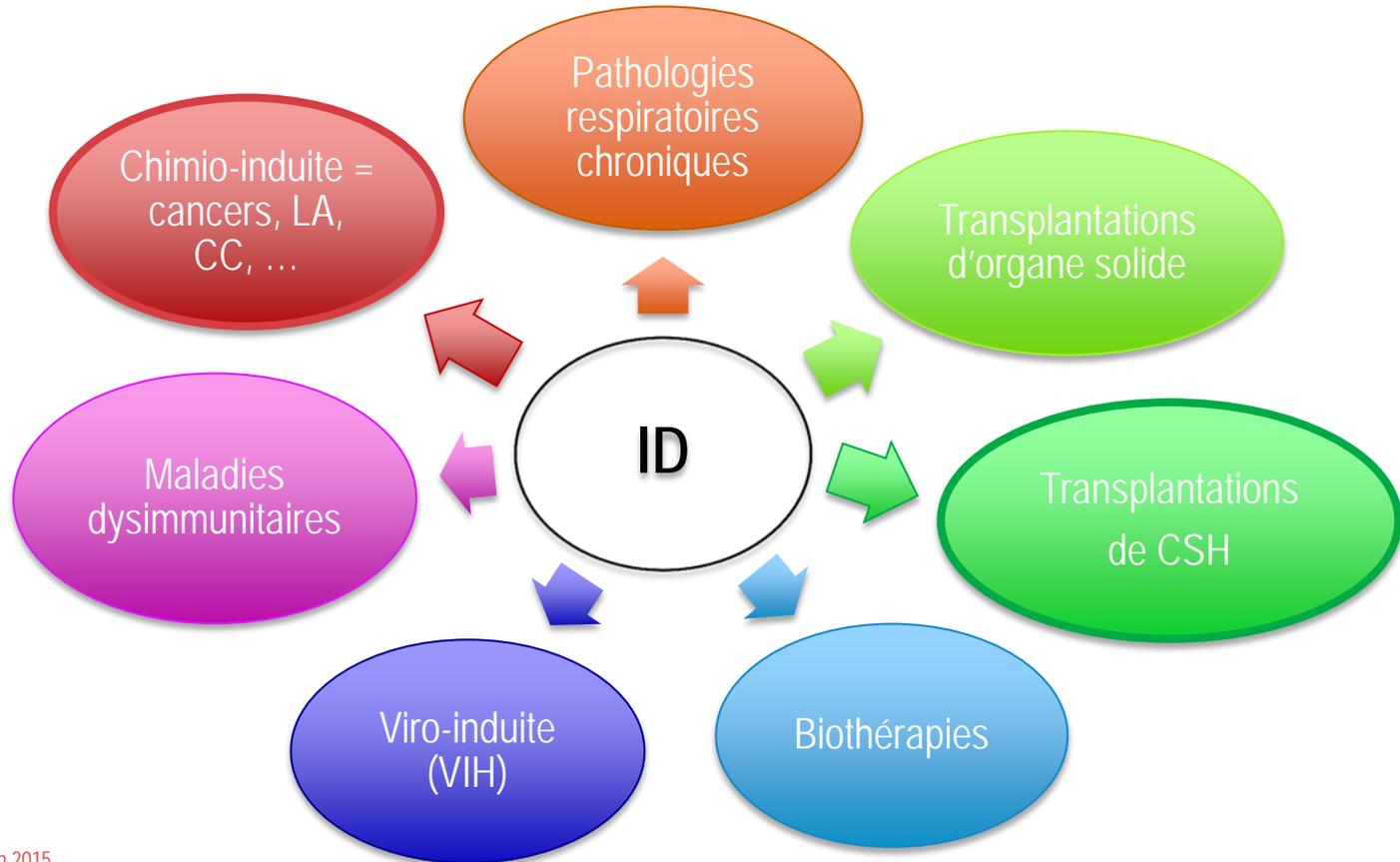


# Infections fongiques invasives chez l'immunodéprimé : le point du vue du clinicien

Florence Ader

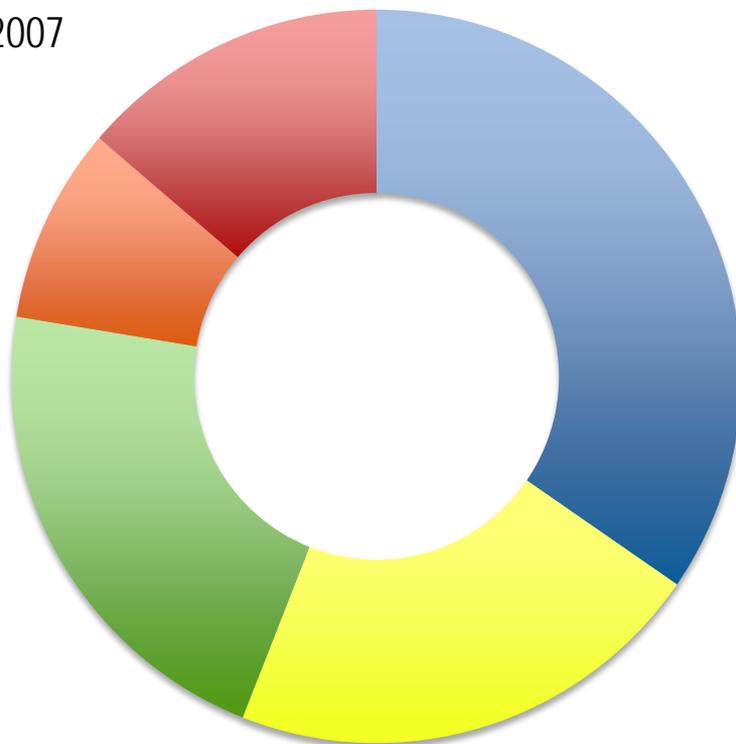
Service des Maladies Infectieuses et Tropicales, Hospices Civils de Lyon  
Inserm 1111 Centre International de Recherche en Infectiologie (CIRI), UCBL1  
Lyon HEMINF study group

# Le spectre d'hôtes



# Aspergillose invasive

SAIF Study 2005-2007



■ Leucémies aiguës

■ Transplantations de CSH

■ Hémopathies lymphoïdes

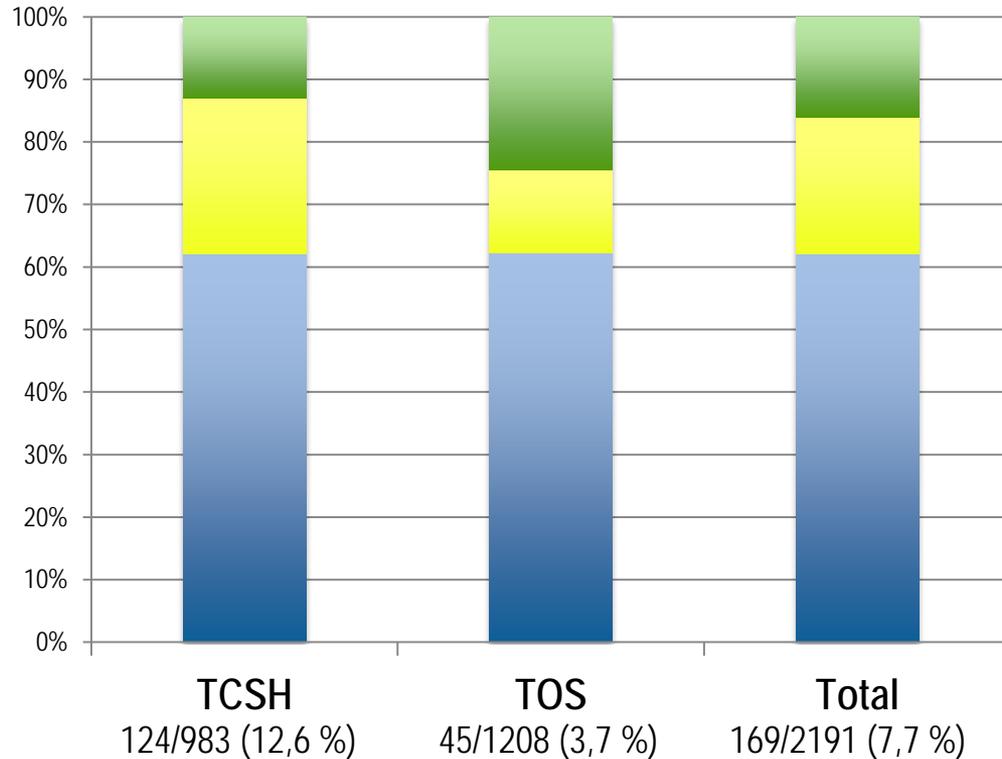
■ Transplantations d'organe solide

■ Autres

**77,6%**

*Lortholary et al., Clin Microbiol Infect 2011*

# IFI émergentes prouvées ou probables



USA

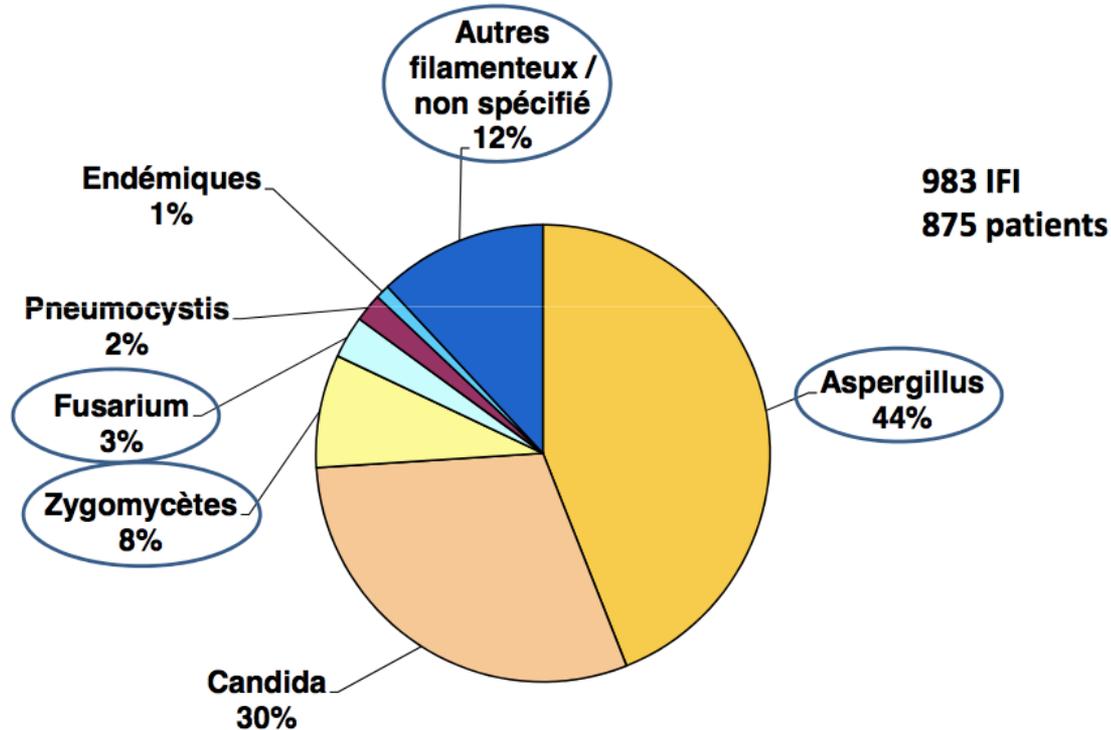
Réseau TRANSNET 2001-2006

n = 23 centres

- Genus Scedosporium
- Genus Fusarium
- Mucorales

*Park BJ et al., Emerg Infect Dis 2010*

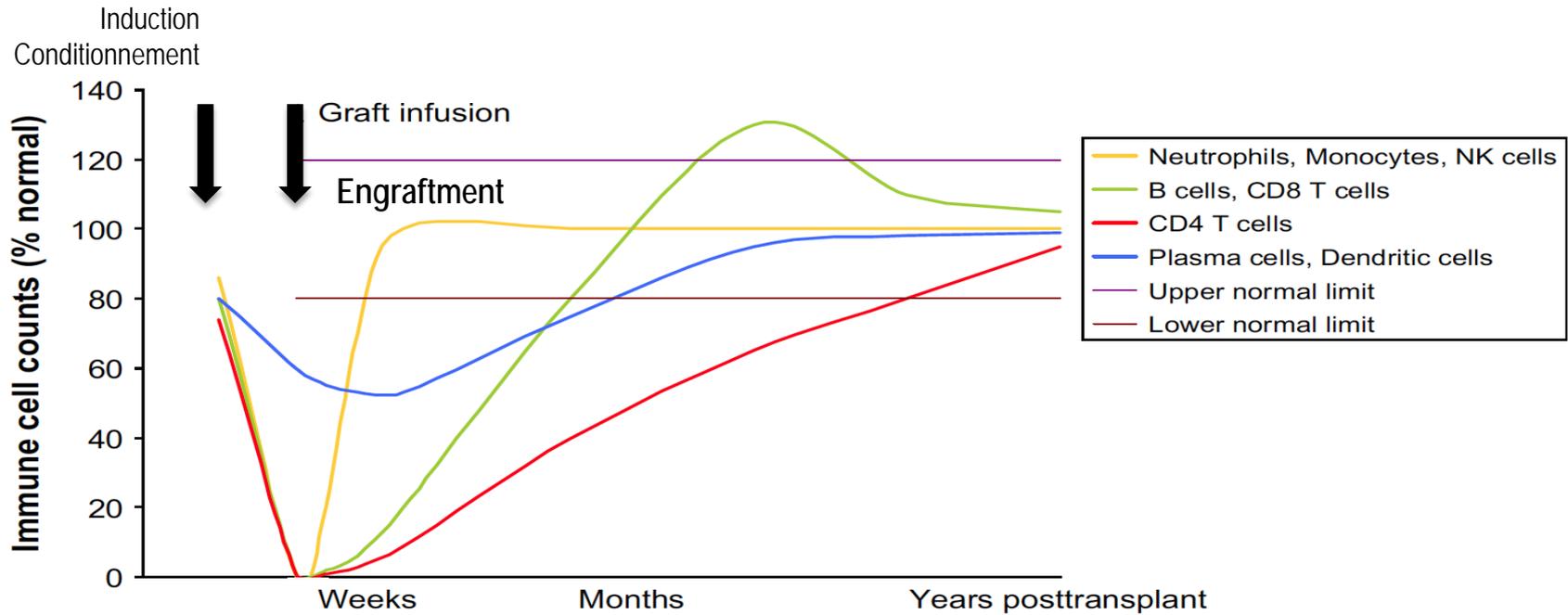
## 16 200 TCSH de 2001 à 2005



# Hématologie/IFI : les questions pertinentes pour le clinicien

1. Neutropénie
2. Transplantation allogénique de CSH ?
3. GvHD et son traitement?
4. Prophylaxie antifongique ?
5. Mesures d'isolement ?

# Reconstitution immunitaire post-TCSH

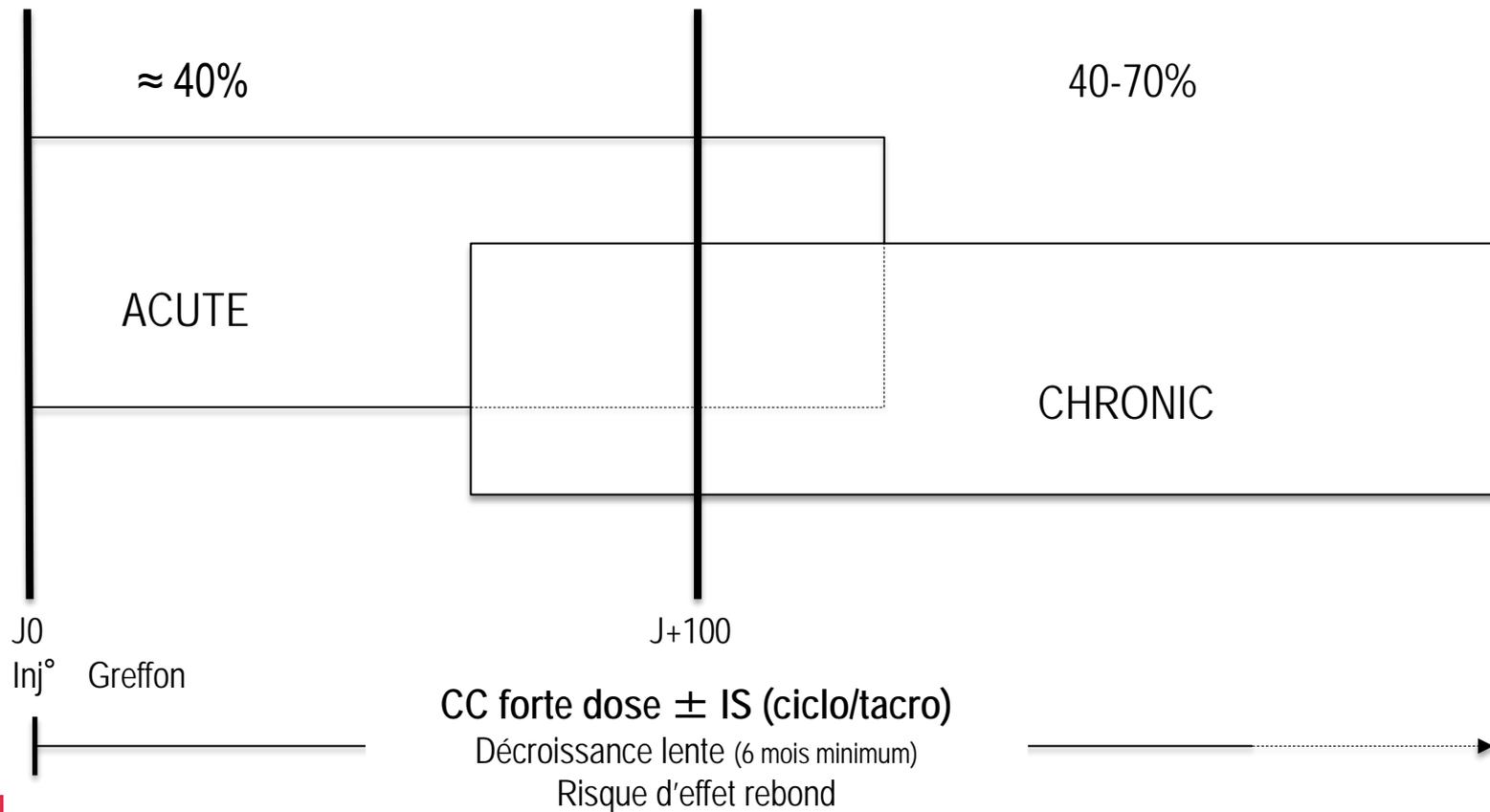


*Tomblyn et al., Biol Bone Marrow transplant 2009*

*From Storek J. Immunological reconstitution after hematopoietic cell transplantation—its relation to the contents of the graft.*

*Expert Opin Biol Ther (Informa). 2008;8:583-597.*

# Graft versus host disease (GvHD)



30% de mortalité reliée  
(directe/indirecte)

# Prophylaxie antifongique large spectre

## Centre-dépendant

Prescrivez-vous une prophylaxie antifongique à spectre large dans les cas suivants ?

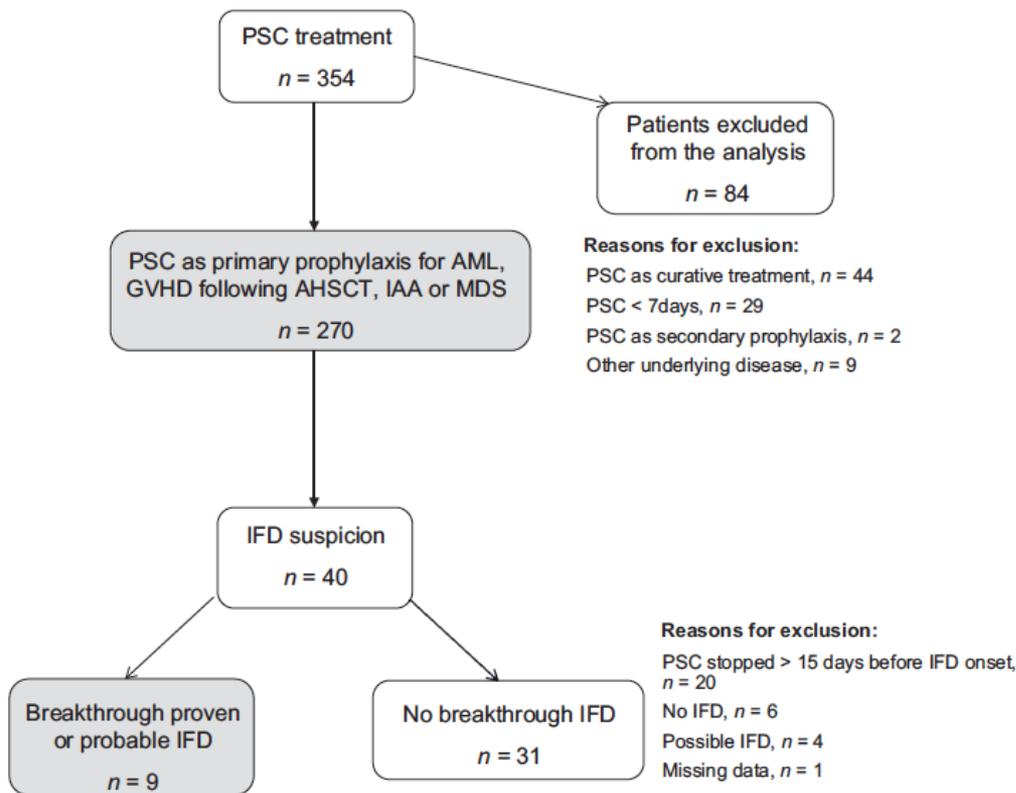
HEMOPATHIE					GREFFE CSH		CHIMIO THERAPIE		FACTEUR DE RISQUE présent ou prévu			
LAL	LAM	MDS	Lymphoïde	Aplasie Med. Idiop.	Allo	Auto	Induc	Cons	Neutropénie	GVH I-II	GVH III- IV	Cort.
27%	90%	58%	4%	42%	46%	8%	90%	65%	58%	23%	61%	50%

Analyse de la prévention des IFI invasives en Hématologie. Enquête des pratiques en France dans des centres adultes (2009-2010)

Centres: *Dijon, Saint-Etienne, Mulhouse, Lille, Clermont-Fd, Saint-Louis, Marseille (IPC), Lyon, Poitiers, Nice (Antoine Lacassagne), Toulouse, Reims, Grenoble, Rennes, CLB Lyon, Liège, Angers, Versailles, Rouen, Besançon, Brodeaux, Montpellier, Limoges, Amiens, Strasbourg*

*Données Pr M. Michallet – Hématologie CHU de Lyon*

# IFI émergentes et prophylaxie large spectre anti-filamenteuse



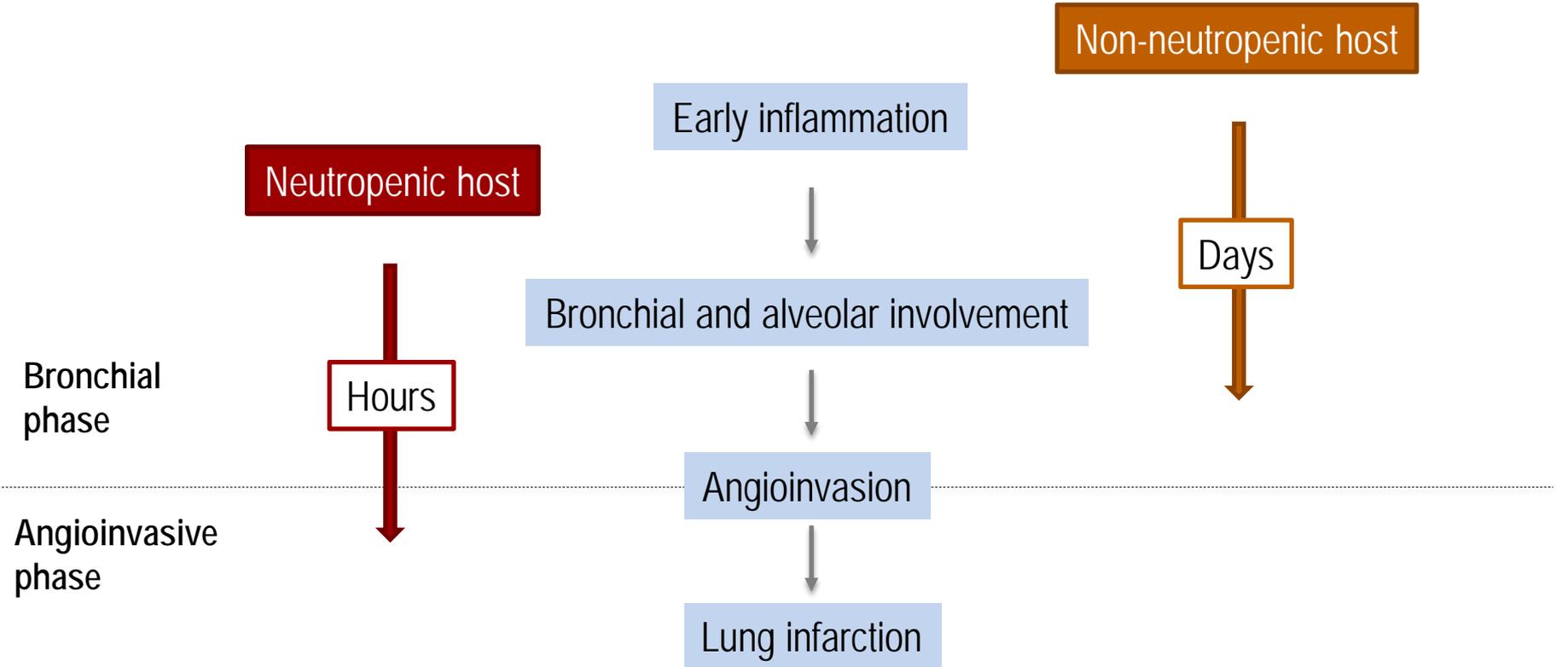
France  
Rétrospectif, monocentrique  
4 ans  
PSC susp. buv.  
 $n = 9$

- . 2 candidémies
- . 3 API
- . 2 mucormycoses pulmonaires
- . 2 fusarioses disséminées

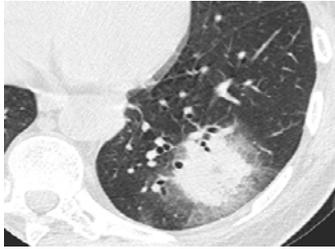
*Lerolle N et al., Clin Microbiol Infect 2014*

**+ IFI possibles !!!**

# Focus 1. Typologies de l'AI



## Angio-invasive



Nodule with halo sign



Air crescent-Cavity  
Dissemination

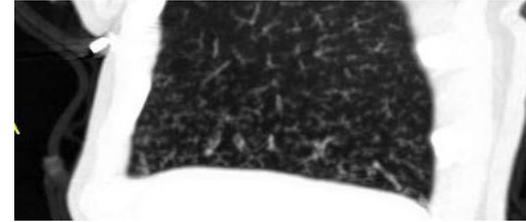
### Neutropenic host

Acute leukemia  
Allo-HSCT pre-engraftment period

## Bronchial or airway-invasive

Ground glass opacities

Bronchiectasis



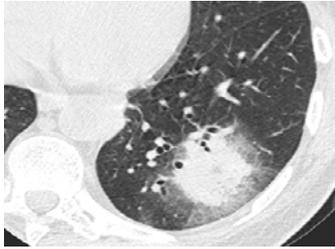
Tree-in-bud opacities

### Non-neutropenic host

Allo-HSCT  
GVHD

Solid organ transplant

## Angio-invasive



Nodule with halo

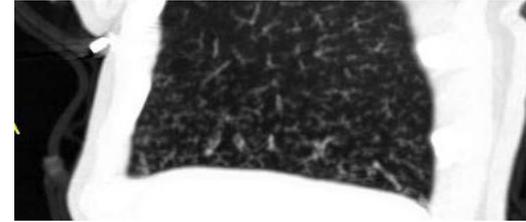


Air crescent-Cavity  
Dissemination

## Bronchial or airway-invasive

Ground glass opacities

Bronchiectasis



Tree-in-bud opacities

*Aspergillus* GM

Bronchial side

Vascular side

*Aspergillus* GM



Nodule with a **halo sign** revealing **angioinvasive** aspergillosis in an AL patient



Centrilobular nodules and **tree-in-bud opacities** showing **airway-invasive** aspergillosis in a patient who underwent an allogeneic HSCT

# The strategy for the diagnosis of IPA should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies

The **neutrophil count** drives the predominant pattern of IPA

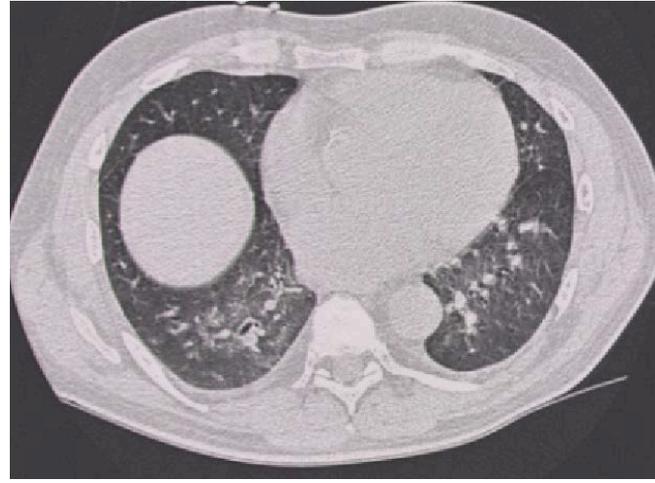
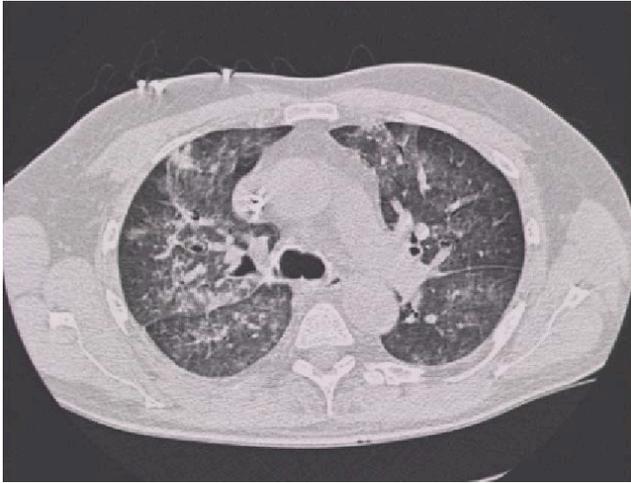
	Leukocyte count < 100/mm <sup>3</sup> (n = 27)	Leukocyte count > 100/mm <sup>3</sup> (n = 28)	P
Angioinvasive disease* (n = 140)	13	1	.001
At least 1 airway-invasive sign (n = 22)	4	18	.001
Airway-invasive disease† (n = 15)	2	13	.005

\* At least 1 nodule with halo sign and no sign of airway-invasive disease.

† Centrilobular micronodules and/or tree-in-bud without any nodule with halo sign

Angioinvasive pattern = **45% of AL patients** vs. 13% of allo-HSCT recipients

Airway-invasive pattern = **44% of allo-HSCT recipients** vs. 14% of AL patients



Patient allo-HSCT avec GvHD chronique et corticoïdes sous prophylaxie anti-filamenteuse avec toux et fièvre

Serum GM = 0.1 – BAL GM 3.7

*Images courtesy of J. Maertens*

# *Aspergillus galactomannan (GM)*

Significant inverse correlation between neutrophil count and serum GM

*Cordonnier et al., Clin Microbiol Infect 2009*

Neutropenic patients  
Serum GM x3/week



Allo-HSCT patients  
GM in BALF  
Optimal cutoff value of 1.0

*Hong Nguyen et al., ASBMT 2010*

*Zou et al. PLoS One 2012*

*Nucci et al., Haematologica 2013*

**Cross-reactivity**

*Fusarium spp./Aspergillus GM assay*

*Tortorano et al., J Clin Microbiol 2012*

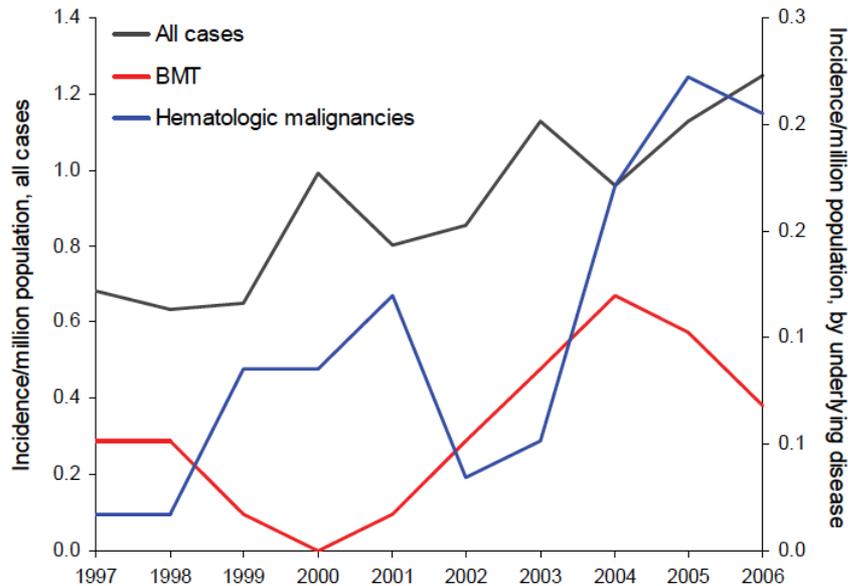


Nodule solitaire sous prophylaxie anti-filamenteuse  
API **possible** ou autre IFI émergente ?  
(mucormycose, fusariose, autre....)

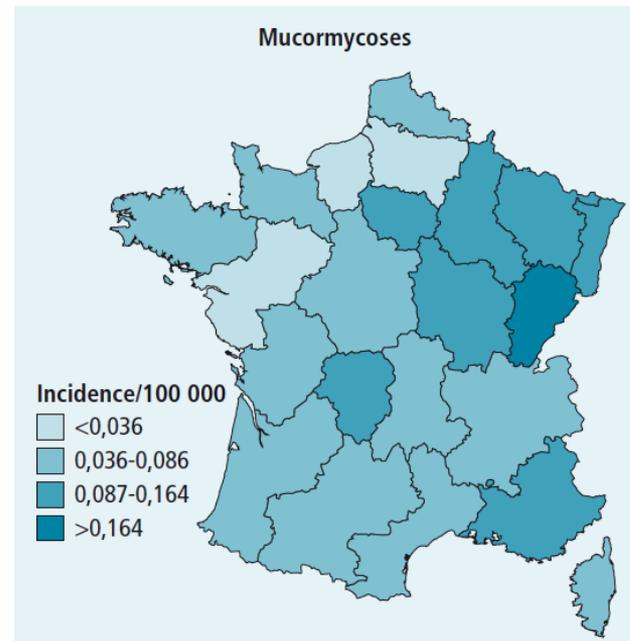
*Image from Wingard JR, Blood 2012*

# Focus 2. Mucormycoses

# Mucormycoses



Bitar D et al., *Em Infect Dis* 2009



PMSI 2001-2010

Bitar D et al., *BEH* 2013

# Mucormycoses : les questions pertinentes pour le clinicien

Outre :

1. Neutropénie
2. Transplantation allogénique de CSH ?
3. GvHD et son traitement?
4. Prophylaxie antifongique ?
5. Mesures d'isolement ?

Verifier :

- 6. Diabète**
- 7. Symptomatologie ophtalmo + ORL**

# Manifestations cliniques des mucormycoes

RetroZygo study: 101 cases of proven (n=60) and probable (n=41) mucormycosis

	No.(%) of Patients With Each Underlying Factor				
	Hematological Malignancy (n = 50)	Diabetes Mellitus (n = 23)	Trauma (n = 18)	SOT (n = 3)	Other (n = 7)
Lung	22 (44)	3 (13)	0	1	2
Rhinocerebral	6 (12)	16 (70)	1 (6)	0	2
Cutaneous	4 (8)	0	15 (83)	0	1
Disseminated	13 (26)	2 (9)	1 (6)	1	1
Other	5 (10)	2 (9)	1 (6)	1	1

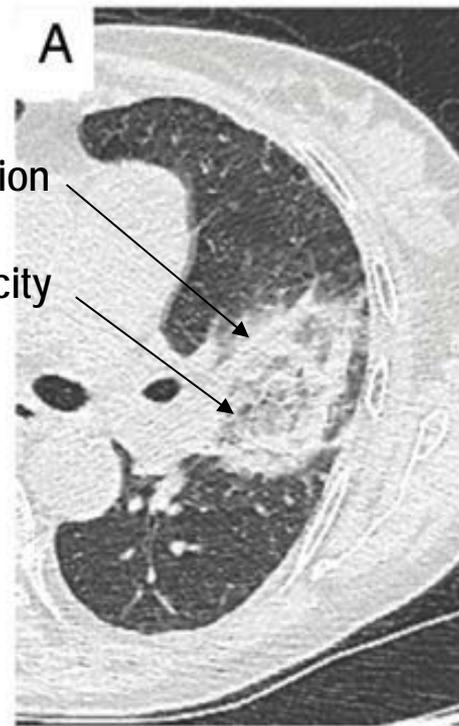
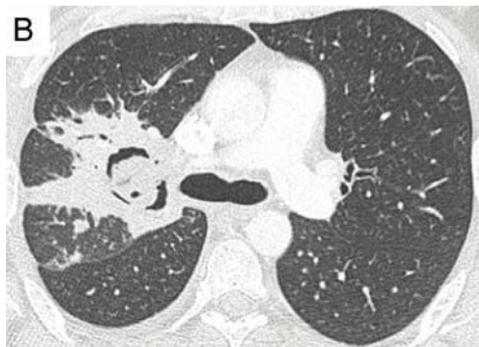
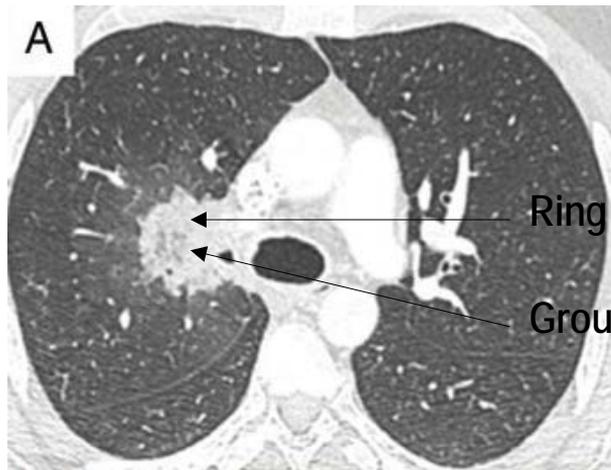
Mortalité J+90 = 56%

Pronostic aggravée si dissémination

*Lanternier F et al. Clin Infect Dis 2012*

# Mucormyose pulmonaire: signe du halo inversé

2003-2012  
Monocentrique  
LA  
n = 16  
SHI 15/16 (94%)



*Legouge C et al., Clin Infect Dis 2014*

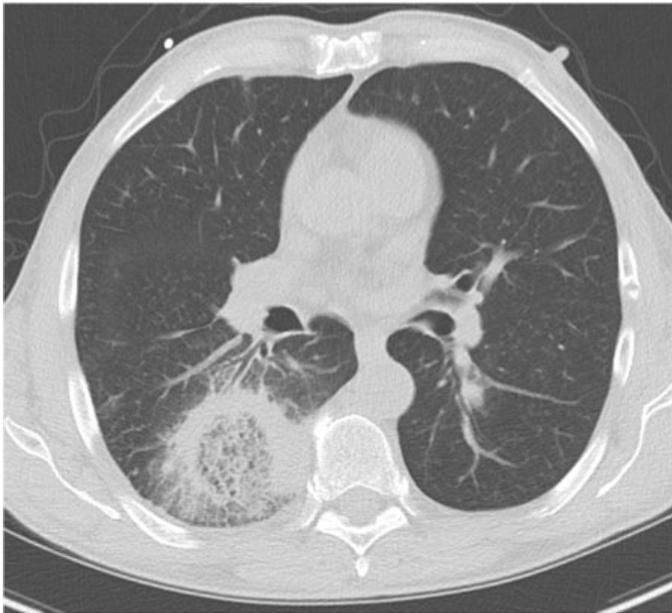
# Mucormyose pulmonaire: signe du halo inversé

Fungal infections
Mucormycosis <sup>a</sup>
Invasive aspergillosis
Paracoccidioidomycosis
Bacterial infections
Slow-resolving pneumococcal pneumonia
<i>Chlamydia psittaci</i>
<i>Legionella pneumophila</i>
Mycobacterial infections
<i>Mycobacterium tuberculosis</i>
Systemic diseases
Wegener granulomatosis
Sarcoidosis
Churg–Strauss syndrome
Dermatomyositis
Neoplastic diseases
Lymphomatoid granulomatosis
Various pulmonary diseases
Cryptogenic organizing pneumonia <sup>b</sup>
Acute fibrinous and organizing pneumonia
Lipoid pneumonia

→ Etiologie la plus fréquente chez l'ID

→ Etiologie la plus fréquente chez l'IC

# Signe du halo inversé



*Georgiadou SP et al. Clin Infect Dis. 2011*  
*Marchiori E et al., Chest 2012*  
*Juan YH. QJ Med 2014*

Population	Intention	Method / Finding	SoR	QoE
Patients with haematologic malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT / reversed halo	B	IIu

*ESCMID and ECMM Joint Clinical Guidelines for the Diagnosis and Management of Mucormycosis 2013  
Cornely O et al., Clin Microbiol Infect 2013*

# Mucormycoses rhinocérébrales

Extension régionale vers nez, palais, orbite

Angio-invasion = thrombophlébite (sinus caverneux),  
ischémie cérébrale

# CT imaging



Images provided by F. Lanternier

# Endoscopie



Image provided by F. Lanternier

# Traitement des mucormycoses

Recommandations	Niveau
Association : contrôle des facteurs de risque, traitement antifongique, chirurgie	AII
<b>Traitement antifongique</b>	
• Amphotéricine B déoxycholate	CII <sup>1</sup>
• Amphotéricine B liposomale®	BII <sup>1</sup>
• ABLC (Abelcet®)	BII
• Posaconazole 400 mg/12 heures	CIII <sup>2</sup>
• Association d'antifongiques	CIII
<b>Contrôle des facteurs de risque sous-jacents</b>	AII <sup>3</sup>
<b>Recours chirurgical selon la localisation infectieuse</b>	
1. Rhino-orbito-cérébrale	AII
2. Tissu mou	AII
3. Pulmonaire	BII
4. Disséminée	CIII <sup>4</sup>
<b>Oxygénothérapie hyperbare</b>	CIII

→ ≥ 5 mg/kg/j – 10 mg/kg/j

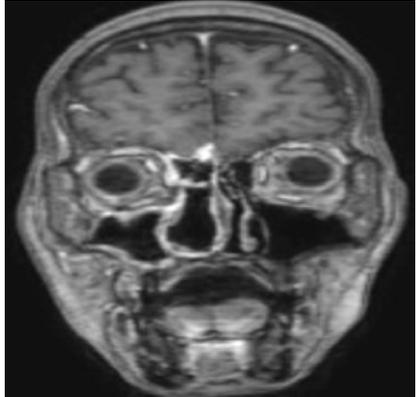
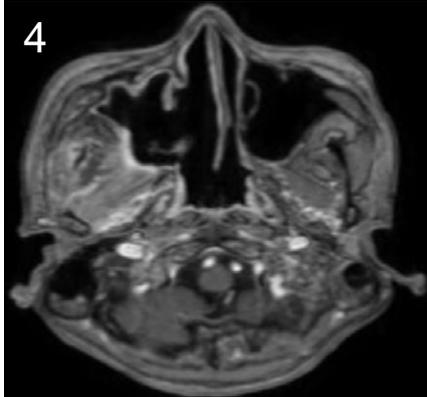
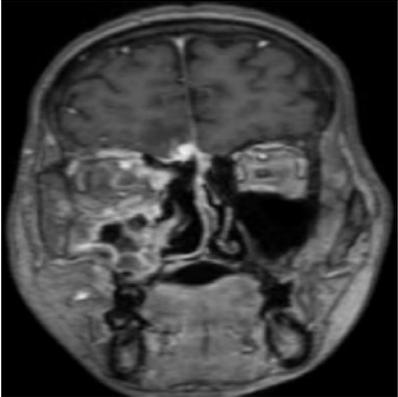
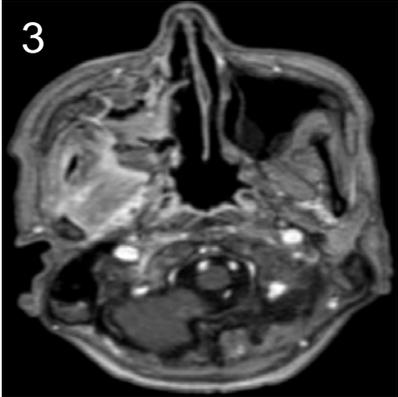
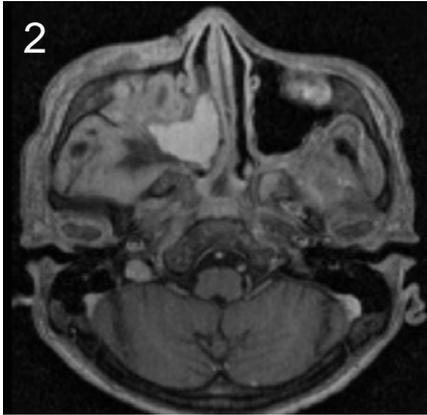
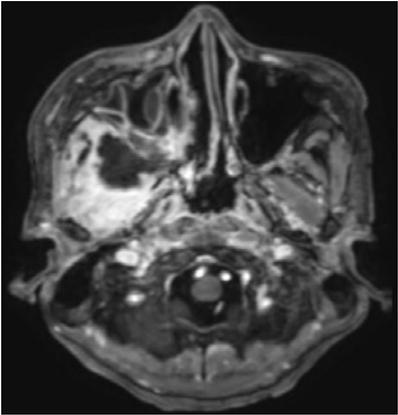
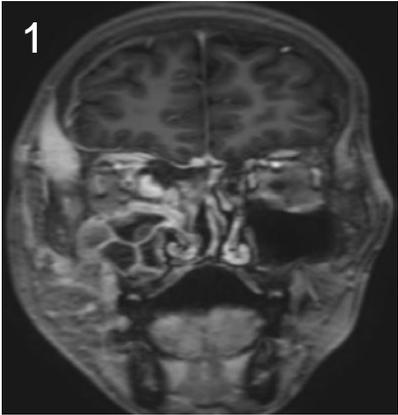
# Importance de la chirurgie dans les mucormycoses rhinocérébrales

Population	Intention	Intervention	SoR	QoE	Comment	Reference
Any	To increase survival rates	Surgical debridement	A	Ilu	N=32	[120]
					N=90	[3]
					N=45	[38]
					N=9	[7]
					N=59	[25]
					N=92, paediatric	[121]
Any	To cure and to increase survival	Surgical debridement in addition to antifungal	A	Ilu	N=470	[3]
					N=19	[122]
					N=90	[7]
					N=92, paediatric	[121]

**Chirurgies itératives**

*ESCMID and ECMM Joint Clinical Guidelines for the Diagnosis and Management of Mucormycosis 2013  
Cornely O et al., Clin Microbiol Infect 2013*

# Par extension, importance de la chirurgie dans les IFI rhinocérébrales ?



# Focus 3. Fusarioses

Onychomycose de l'immunocompétent

Keratite à *Fusarium* spp. (lentilles de contact)



Keratite à *Fusarium* spp. avec hypopyon

# Fusarioses : les questions pertinentes pour le clinicien

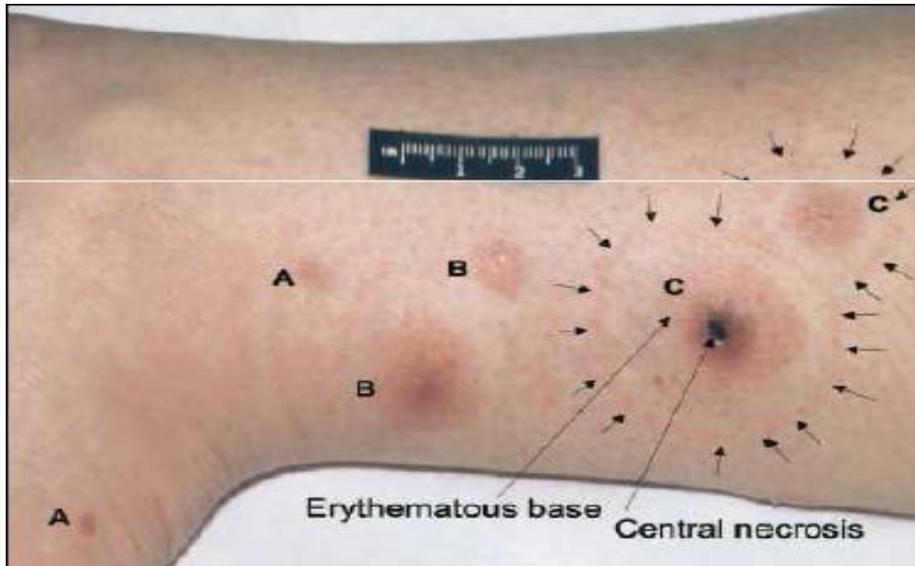
Outre :

1. Neutropénie
2. Transplantation allogénique de CSH ?
3. GvHD et son traitement?
4. Prophylaxie antifongique ?
5. Mesures d'isolement ?

Verifier :

- 6. Antécédents infections cutanées**
- 7. Onychomycose**

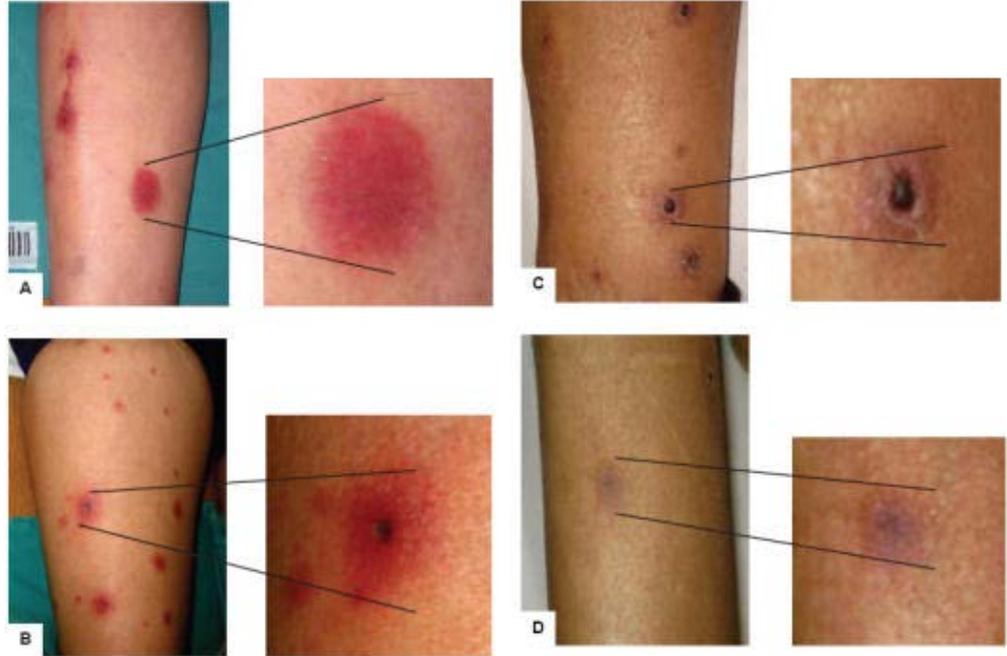
# Fusariose



Courtesy of Nucci M



Nucci M et al., *Emerg. Infect Dis* 2013



*Mehta A & Bellam N. Blood 2014*

*Stanzani M et al., Ther Clin Risk Manag. 2007*

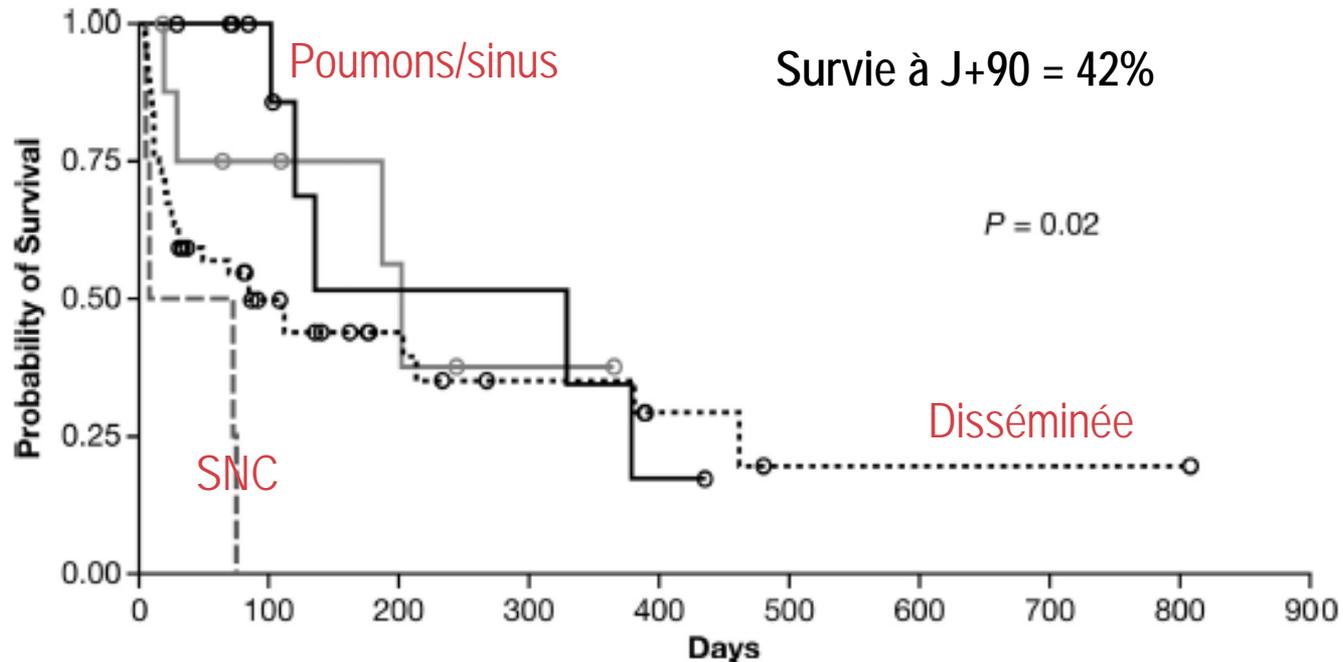
Characteristic	Total, N = 233	Period 1, N = 121	Period 2, N = 112	p-Value
Skin involvement	143 (61)	70 (58)	73 (65)	0.25
Lung involvement	114 (49)	60 (50)	54 (48)	0.83
Sinusitis	72 (31)	34 (28)	38 (34)	0.34
Fungaemia	86 (37)	31 (26)	55 (49)	<0.001
Disseminated disease	166 (72)	89 (74)	77 (69)	0.48

Nucci et al., Clin Microbiol Infect 2014

Factor	AML (n = 8)	Allo Phase 1 (n = 10)	Allo Phase 2 (n = 5)	Auto (n = 2)
Predisposing factors, No.				
Neutropenia	8	10	1	2
Receipt of corticosteroids	1	7 <sup>a</sup>	5 <sup>b</sup>	2
Manifestations, No.				
Fever	8	9	2	2
Skin lesions	6	6	5	1
Pneumonia	6	5	2	0
Sinusitis	3	3	1	0
Fungemia	2	5	1	1
Arthritis	0	1	2	0
CNS involvement	0	0	1	0
Endophthalmitis	1	1	0	0

Nucci et al., Clin Infect Dis 2015

n = 73; cerveau (5%), disséminée non cérébrale (67%), poumons/sinus (15%)



Lortholary O et al, Antimicrobial Ag Chemother 2010

# Etude rétrospective internationale

## Neutropénie 64%

Underlying condition (no. of patients)	Median (range) duration of voriconazole therapy (days)	No. (%) with clinical response	Median (range) survival (days)	No. that died (no. that died due to IFI)
HSCT (13)	18 (3–182)	5 (38)	27 (6–202)	9 (4)
HM <sup>a</sup> (44)	61 (1–480)	20 (45)	112 (4–808)	27 (15)
Chronic <sup>b</sup> (9)	57 (3–267)	4 (44)	200 (6–435)	5 (3)
Other <sup>c</sup> (7)	30 (19–259)	5 (71)	Not reached (19–365)	2 (0)
Total (73)	57 (1–480)	34 (47)	120 (4–808)	43 (22)

<sup>a</sup> HM, hematologic malignancy.

<sup>b</sup> Chronic conditions included lymphoma (3 patients), aplastic anemia (3), tumor lysis syndrome (1), neuroblastoma (1), and kidney transplant (1).

<sup>c</sup> Other conditions were immunocompetence (4 patients), diabetes mellitus (2), paralytic ileus (1), and burns (1).

# Bilan *simili*-IFI à levures

HC quantitatives : périph et KTC  Dépose KTC impérative !

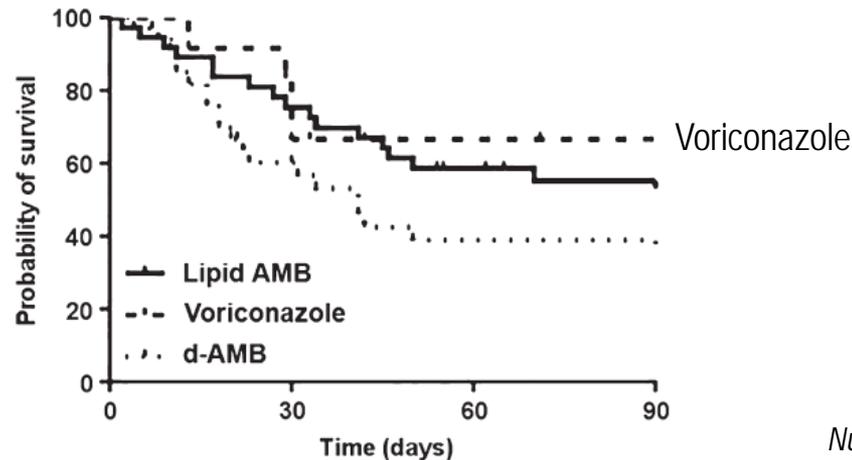
Examen ophtalmologique+++ : fond d'oeil

Body-TDM

# Fusariose : Voriconazole

Site of infection (no. of patients)	Median (range) duration of voriconazole therapy (days)	No. (%) with clinical response	Median (range) survival <sup>a</sup> (days)	No. that died (no. that died due to IFI)
Brain (4)	37 (1-75)	0 (0)	40 (5-75)	4 (4)
Disseminated (49)	33 (3-480)	22 (45)	84 (4-808)	30 (16)
Lung/sinus (11)	90 (24-379)	7 (64)	329 (29-435)	5 (1)
Other <sup>b</sup> (9)	57 (2-259)	5 (56)	202 (19-365)	4 (1)
Total (73)	57 (1-480)	34 (47)	120 (4-808)	43 (22)

*Lortholary O et al, Antimicrobial Ag Chemother 2010*



*Nucci et al., Clin Microbiol Infect 2014*

## **Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience**

NIH case series

1996-2012

11 cas *Fusarium* spp+ prouvés

Gravité++

Leucophérèse HLA compatibilisée

Allo-immunisation n=2 avec 1 perte de greffon

Survie à 1 an 45%

Pas de sortie d'aplasie "autonome" = décès systématique

# *Scedosporium* spp. = résistance à la plupart des ATF

	CMI <sub>90%</sub> (µg/ml)	
	<i>S. apiospermum</i> n=13	<i>S. prolificans</i> n=55
AMB	16	>16
Nys	32	>32
ITZ	4	>32
VRZ	0,5	4
PSZ	2	>8

L'identification d'espèce est importante  
Les CMI doivent être testées pour la souche clinique en cause

## ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others

A. M. Tortorano<sup>1,\*†</sup>, M. Richardson<sup>2,3,\*†,‡</sup>, E. Roilides<sup>4,\*†,‡</sup>, A. van Diepeningen<sup>5,\*</sup>, M. Caira<sup>6,\*</sup>, P. Munoz<sup>7,\*†,‡</sup>, E. Johnson<sup>8,\*†</sup>, J. Meletiadis<sup>9,\*†</sup>, Z.-D. Pana<sup>4,\*</sup>, M. Lackner<sup>10,\*†</sup>, P. Verweij<sup>11,12,\*†,‡</sup>, T. Freiburger<sup>13,\*†</sup>, O. A. Cornely<sup>14,†,‡</sup>, S. Arikan-Akdagli<sup>15,†</sup>, E. Dannaoui<sup>16,†</sup>, A. H. Groll<sup>17,†,‡</sup>, K. Lagrou<sup>18,†</sup>, A. Chakrabarti<sup>19</sup>, F. Lanternier<sup>20,21</sup>, L. Pagano<sup>22,†</sup>, A. Skiada<sup>23,‡</sup>, M. Akova<sup>15,‡</sup>, M. C. Arendrup<sup>24,†,‡</sup>, T. Boekhout<sup>5,25,26,†</sup>, A. Chowdhary<sup>27,‡</sup>, M. Cuenca-Estrella<sup>28,†,‡</sup>, J. Guinea<sup>7,†,‡</sup>, J. Guarro<sup>29,†</sup>, S. de Hoog<sup>5,†</sup>, W. Hope<sup>30,‡</sup>, S. Kathuria<sup>27</sup>, O. Lortholary<sup>31,32,†,‡</sup>, J. F. Meis<sup>11,33,†,‡</sup>, A. J. Ullmann<sup>34,†,‡</sup>, G. Petrikos<sup>35,\*†,‡</sup> and C. Lass-Flörl<sup>10,\*†,‡</sup>

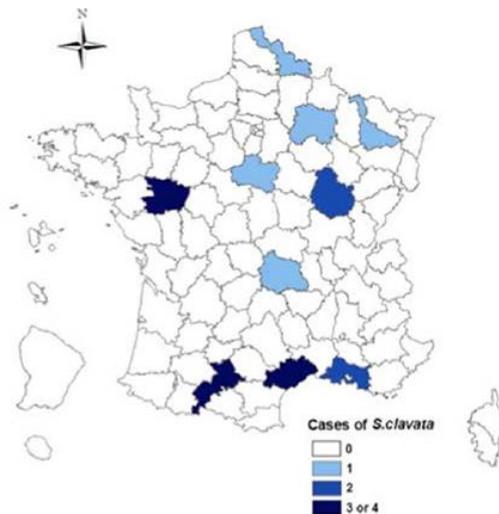
Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients Lung infections	Voriconazole	A	II <sub>c,r</sub>	40% survival Therapeutic drug monitoring	[96,260,261]
	Voriconazole plus terbinafine	B	III	Case reports, 50% survival	[68,91,131,133,262–269]
	Itraconazole	C	III	Case reports, 15% survival	[97,129,263,270]
	Amphotericin B deoxycholate	D	III	Case reports, 4% survival	[118,271–276]
	Any combination	C	III	Case reports only	[86,119,130,277–281]
	Fluconazole	D	III	Case reports	[98,263,275]
	Voriconazole or Posaconazole plus terbinafine (plus granulocyte colony-stimulating factor)	B	III	Case reports	[68,131,269]
	Dissemination	Voriconazole	B	II	
	Voriconazole plus terbinafine or posaconazole	B	III	Review of case series	[68,261,267,282]

Tortorano et al., Clin Microbiol Infect 2014 – ESCMID guidelines

## Multicenter Outbreak of Infections by *Saprochaete clavata*, an Unrecognized Opportunistic Fungal Pathogen

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*Mbio.asm.org* 2014



Sept 2011-Oct 2012

30 cas/22 décès

Dispositif médicaux, produits laitiers ?

CNR Myco

# Conclusions

- Aspergillose invasive : pas qu'une seule typologie
- Mucormycoses: diabète + évaluation rhino-cérébrale  $\pm$  chirurgie
- Fusariose : atteinte cutanée + bilan "levure-like"
- Autre(s) mycose(s) systémiques: CNR Myco

## **MERCI le Lyon HEMINF study group**

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