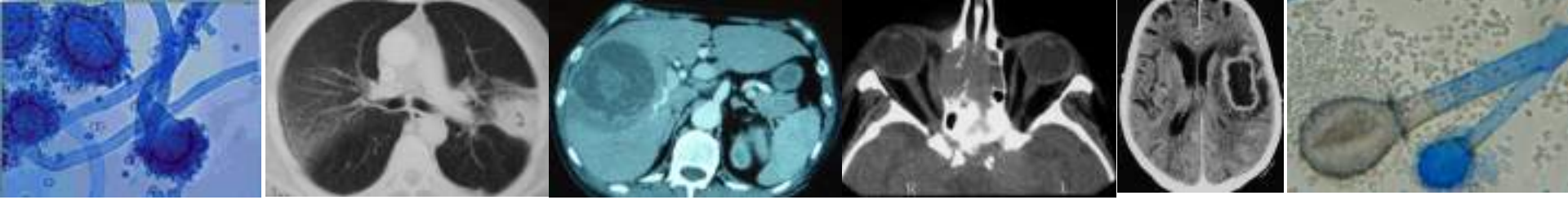


Update on pulmonary fungal infections: perspectives for the chest physician

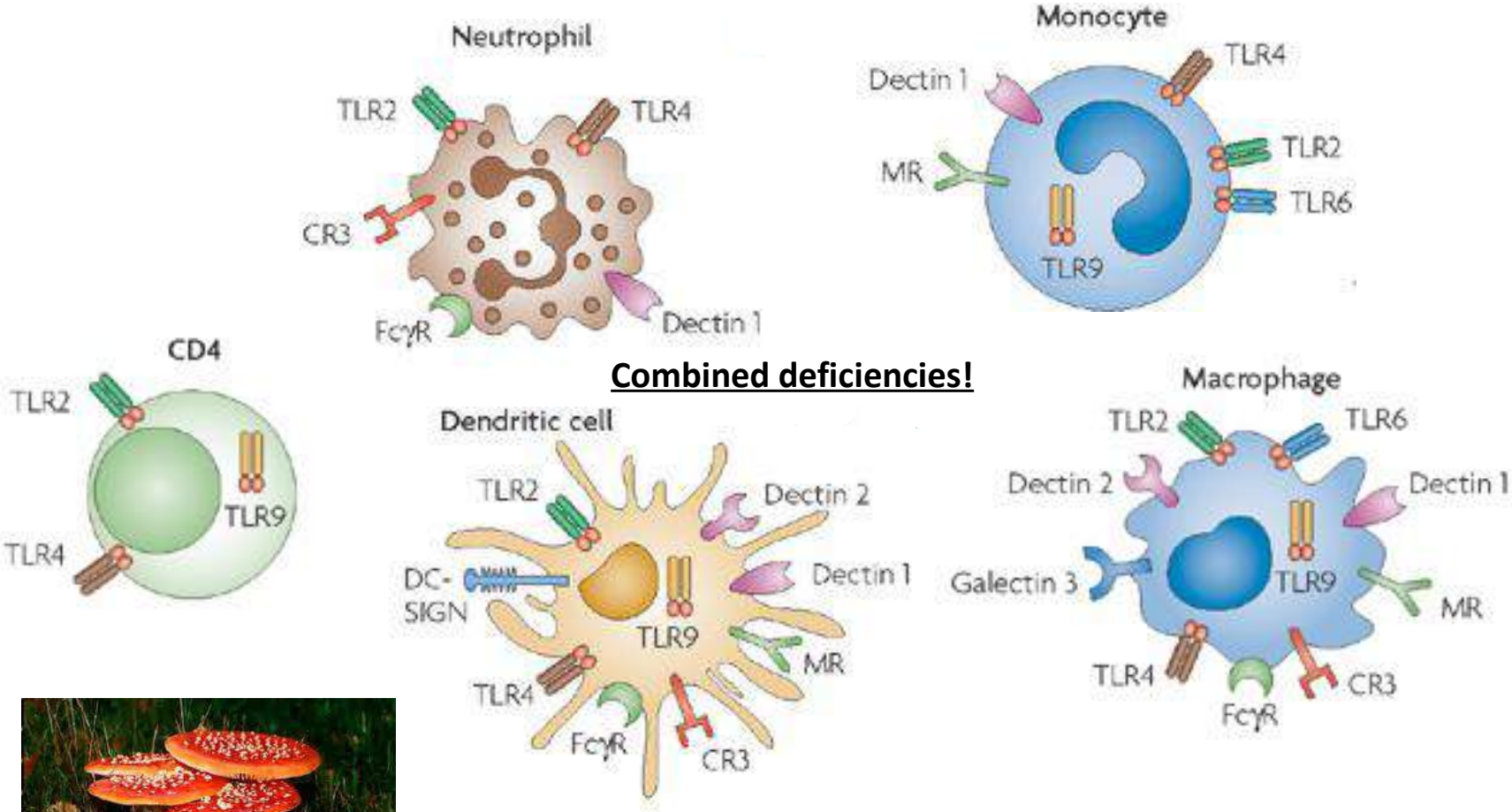
Olivier Lortholary, M.D.; Ph.D

Centre d'Infectiologie Necker-Pasteur
Université Paris Descartes, Hôpital Necker Enfants malades, IHU Imagine &
Centre National de Référence Mycoses Invasives & Antifongiques, Unité de Mycologie Moléculaire, CNRS URA3012, Institut Pasteur, Paris, France.

DES de Pneumologie, 16 février 2018

PARIS DESCARTES · FONDATION imagine · Necker · ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS · Institut Pasteur

Key cells involved in the protection against fungi



Netea Nature Rev Microbiol 2008

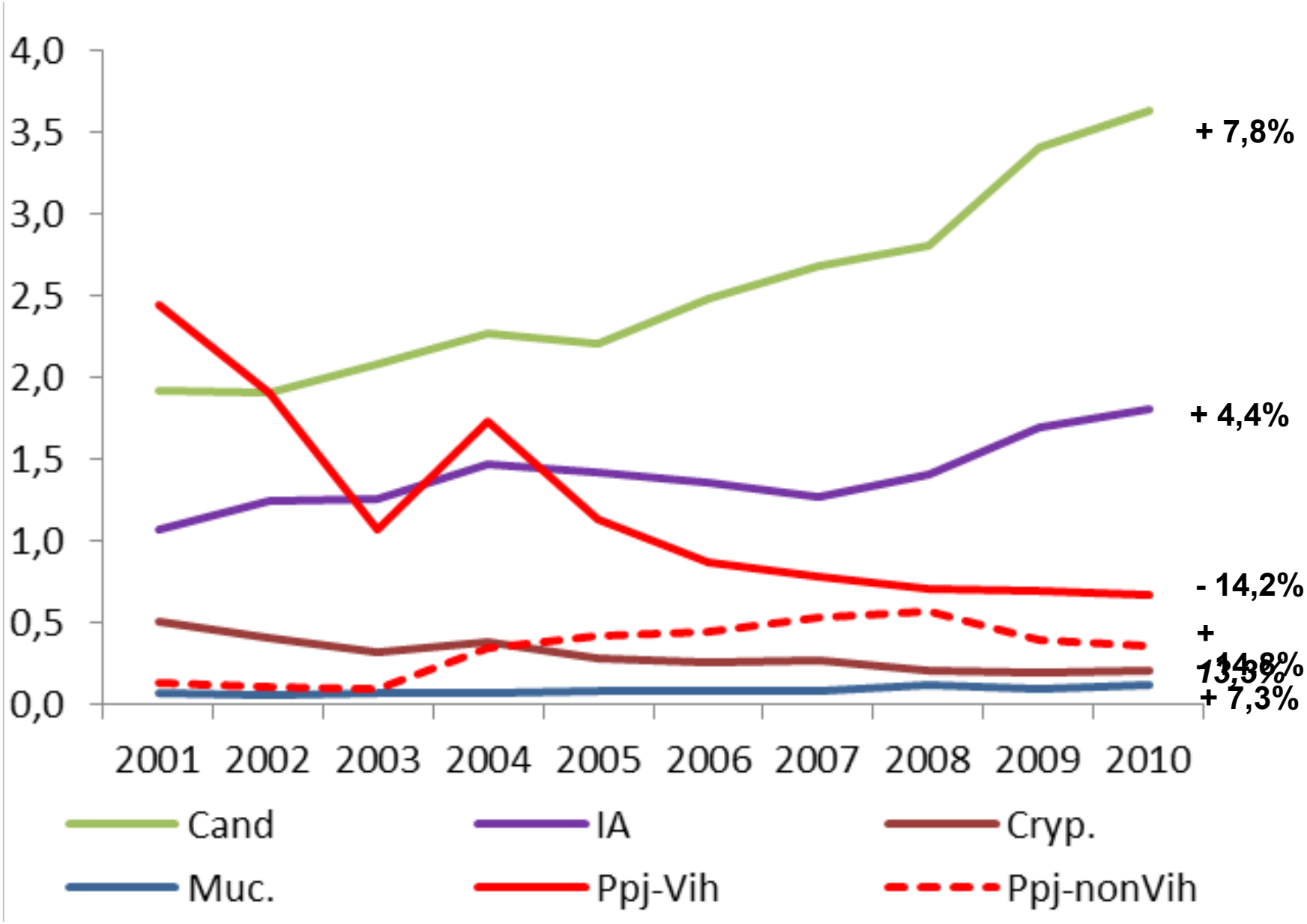
Population-Based Analysis of Invasive Fungal Infections, France, 2001–2010

Dounia Bitar,[1] Olivier Lortholary,[1] Yann Le Strat, Javier Nicolau, Bruno Coignard, Pierre Tattevin, Didier Che,[2] and Françoise Dromer[2]

- N°1: Candidemia (43.4%)
- N°2: *Pneumocystis jirovecii* pneumonia (26.1%)
- N°3: Invasive aspergillosis (23.9%)
- N°4: Cryptococcosis (5.2%)
- N°5: Mucormycosis (1.5%)

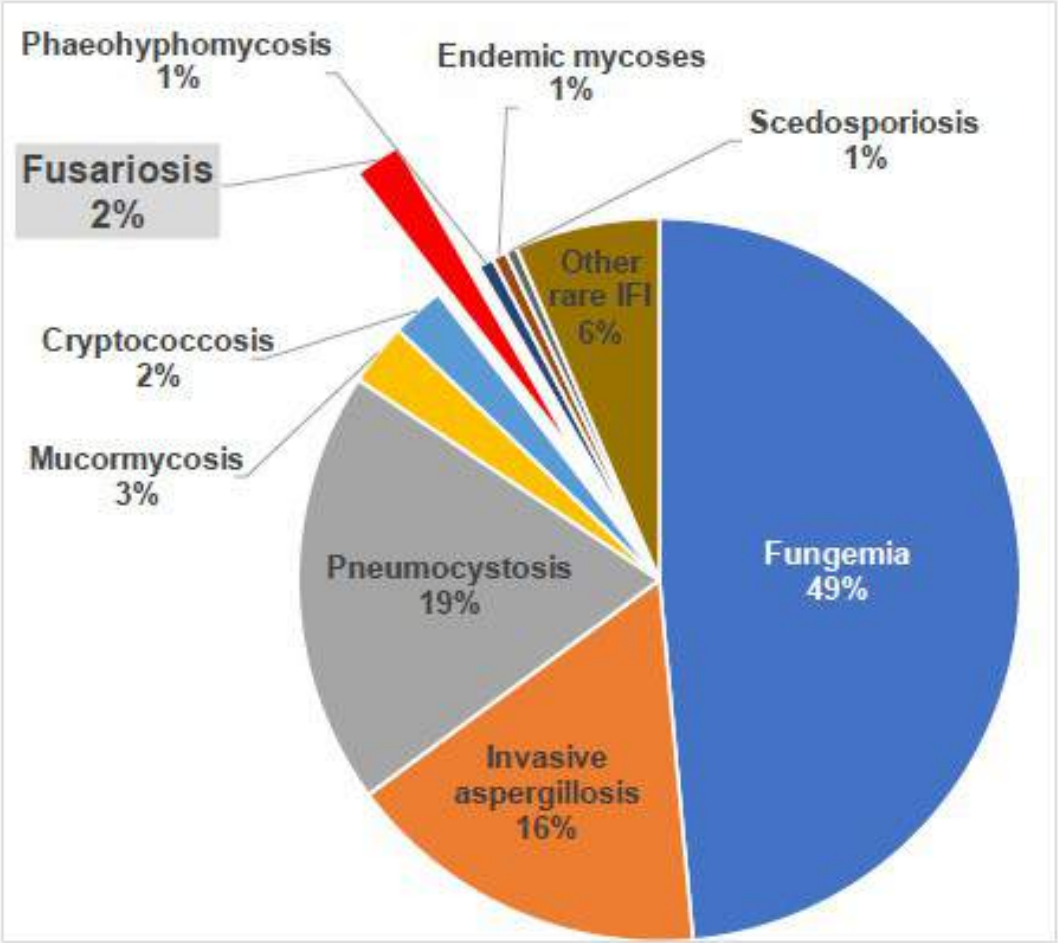
- Invasive aspergillosis 1.8% per 100,000 persons.

Trends of IFI incidence during a decade in France



Bitar, Lortholary et al. Emerg Infect Dis 2014, in press

7,202 IFIs recorded in the RESSIF *active* network (2012-2016)



IFIs=invasive fungal infections

NRCMA, unpublished data

Institut Pasteur

OPEN ACCESS Freely available online

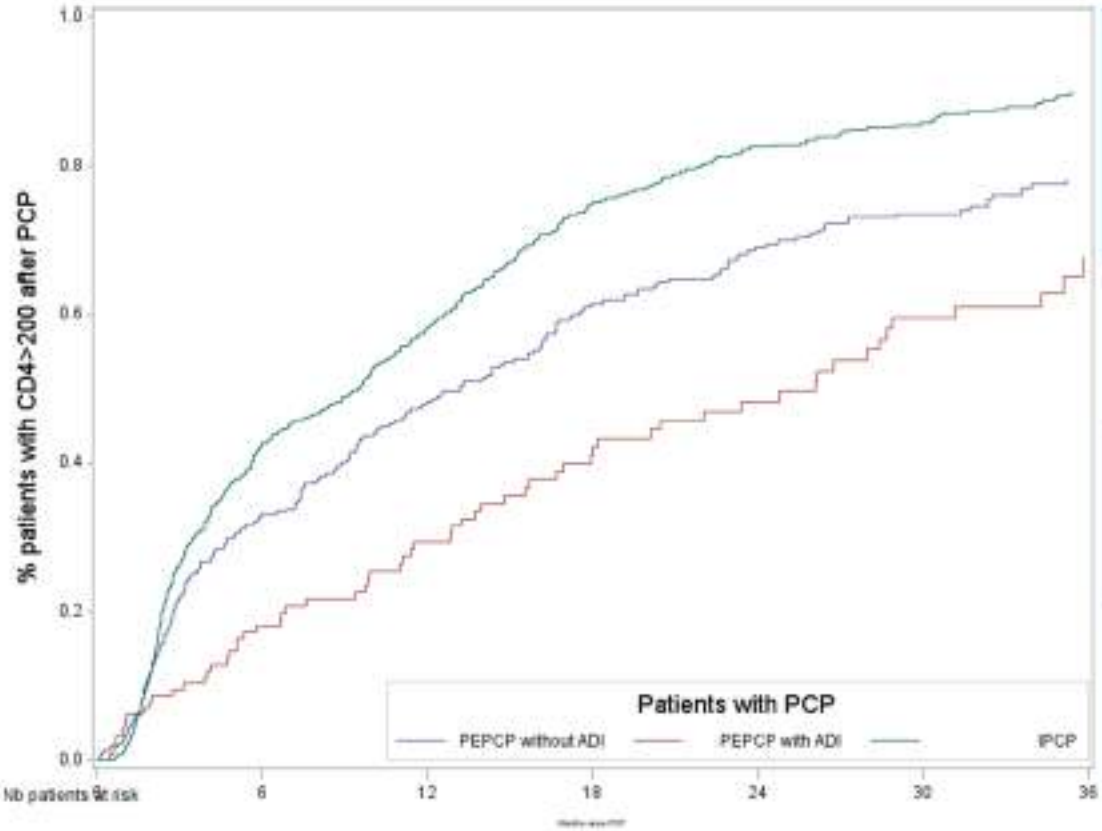
PLOS | ONE

Critical Importance of Long-Term Adherence to Care in HIV Infected Patients in the cART Era: New Insights from *Pneumocystis jirovecii* Pneumonia Cases over 2004–2011 in the FHDH-ANRS CO4 Cohort

Blandine Denis[1,2]*, Marguerite Guiguet[1,2], Nathalie de Castro[3,4], Frédéric Mechaï[5], Matthieu Revest[6], Aba Mahamat[7,8], Giovanna Melica Gregoire[3,4], Olivier Lortholary[9,10,11,12], Dominique Costagliola[1,2]

1 Inserm UMRS 1136, Paris, France, **2** UPMC Univ Paris 06 UMRS 1136, Paris, France, **3** Service de maladies infectieuses et tropicales, CHU Saint Louis, AP-HP, Paris, France, **4** Université Paris Diderot, Paris, France, **5** Service de maladies infectieuses et tropicales, CHU Avicenne AP-HP, Bobigny, France, **6** Service de maladies infectieuses et tropicales, CHU Rennes, Rennes, France, **7** Service de maladies infectieuses et tropicales, CHU Cayenne, Cayenne, France, **8** EA 3595, Univ Antilles-Guyane, Cayenne, France, **9** CHU Necker-Enfants malades, AP-HP, Centre d'Infectiologie Necker Pasteur, Paris, France, **10** Université Paris Descartes, Institut Imagine, Paris, France, **11** Institut Pasteur, Centre National de Référence Mycoses Invasives et Antifongiques, Paris, France, **12** CNRS URA 3012, Paris, France

Slower immune reconstitution for previously enrolled patients



	Immune reconstitution (CD4 >200) Adjusted HR * (95% CI)
Inaugural PCP	1.0
PEPCP without prior ADI	0.7 (0.6 – 0.9)
PEPCP with prior ADI	0.6 (0.4 – 0.8)

* Adjusted on age, transmission group, origin, viral load and CD4 at PCP diagnosis, viral suppression

ADI : Aids Defining Illness, PEPCP : Previously Enrolled

Higher mortality for previously enrolled patients with prior Aids Defining Illness

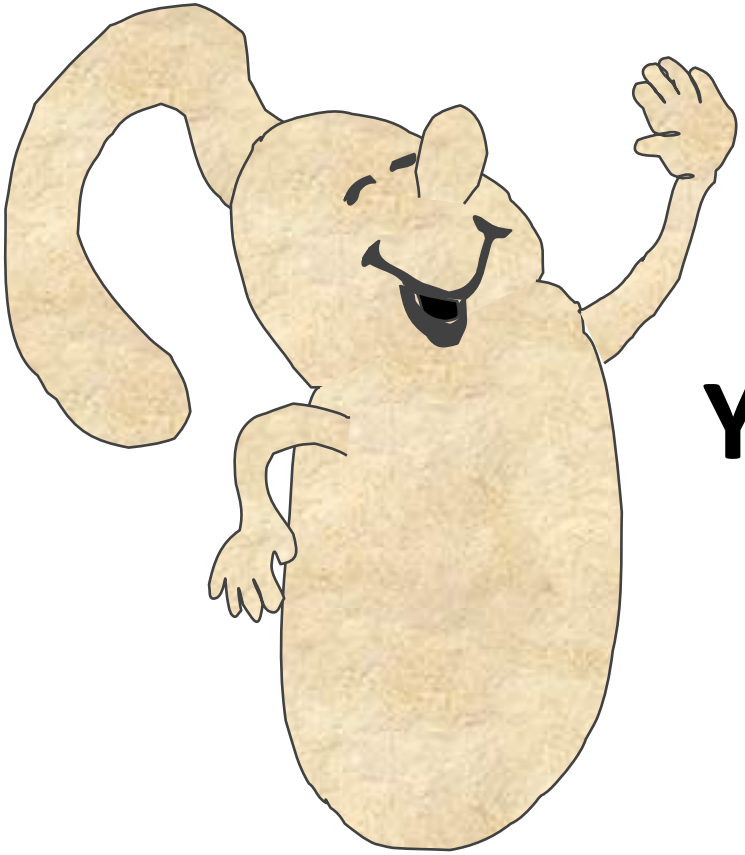
Overall mortality :
After 1 year : 7%
After 3 years : 11%

Mortality at 3 years by subgroup :
- Inaugural PCP :9%
- PEPCP without prior ADI : 8%
- PEPCP with prior ADI : 25%
- ($p<0.0001$)

	Mortality Adjusted HR ** (95% CI)
Inaugural PCP	1.0
PEPCP without prior ADI	0.8 (0.5-1.3)
PEPCP with prior ADI	2.4 (1.5 – 3.7)

** age, transmission group, origin, viral suppression, immune reconstitution

ADI : Aids Defining Illness, PEPCP : Previously Enrolled



Yeasts

Cryptococcus gattii

Emerging yeasts

Cryptococcosis in 2018

Encapsulated yeast : *Cryptococcus neoformans/gattii*

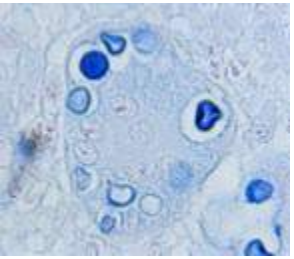
Major risk factor = cellular immune deficiency HIV++

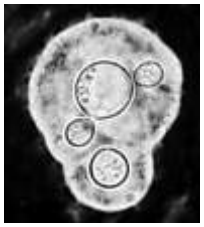
- ❑ AIDS defining illness (extra-pulmonary)
- ❑ 6 % of severely immunodepressed ARV naive patients in Southern & Central Africa/South-East Asia (Bicanic CID 2009; Micol JAIDS 2007; Temfack submitted) :
  - ✓1st cause of meningitis in adults (Africa)
  - ✓4th cause of infectious mortality worldwide (Park, AIDS 2009)
  - ✓Mortality ≥ 50% within first 15d
- ❑ Major impact of antiretroviral therapy

Cryptococcus spp.
an encapsulated environmental yeast

A & D	Serotypes	B & C
neoformans	Species	*gattii* = true species
var. *grubii/neoformans*	Varieties	-
USA-Europe Cosmopolitan (A)	Distribution	Tropical & subtropical
Soil, agrums, Bird droppings	Environment	B : *Eucalyptus* C : Amand trees
Immunocompromised (HIV)	Hosts	±Immunocompetent

C. neoformans infection pathogenesis





Environment

?

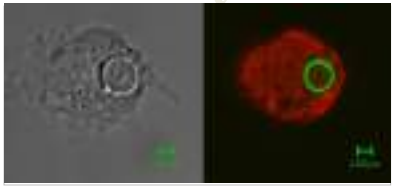
LUNGS
(Alveolar Mphages)

Latency (CD4/Th1 cytok, macrophages)

Immune deficiency

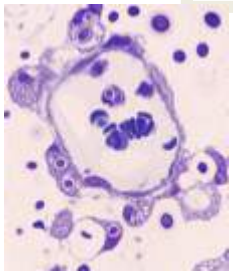
SKIN

Blood (PBMC)



cn

GRAFT



CNS Organs

PRIMARY INF?

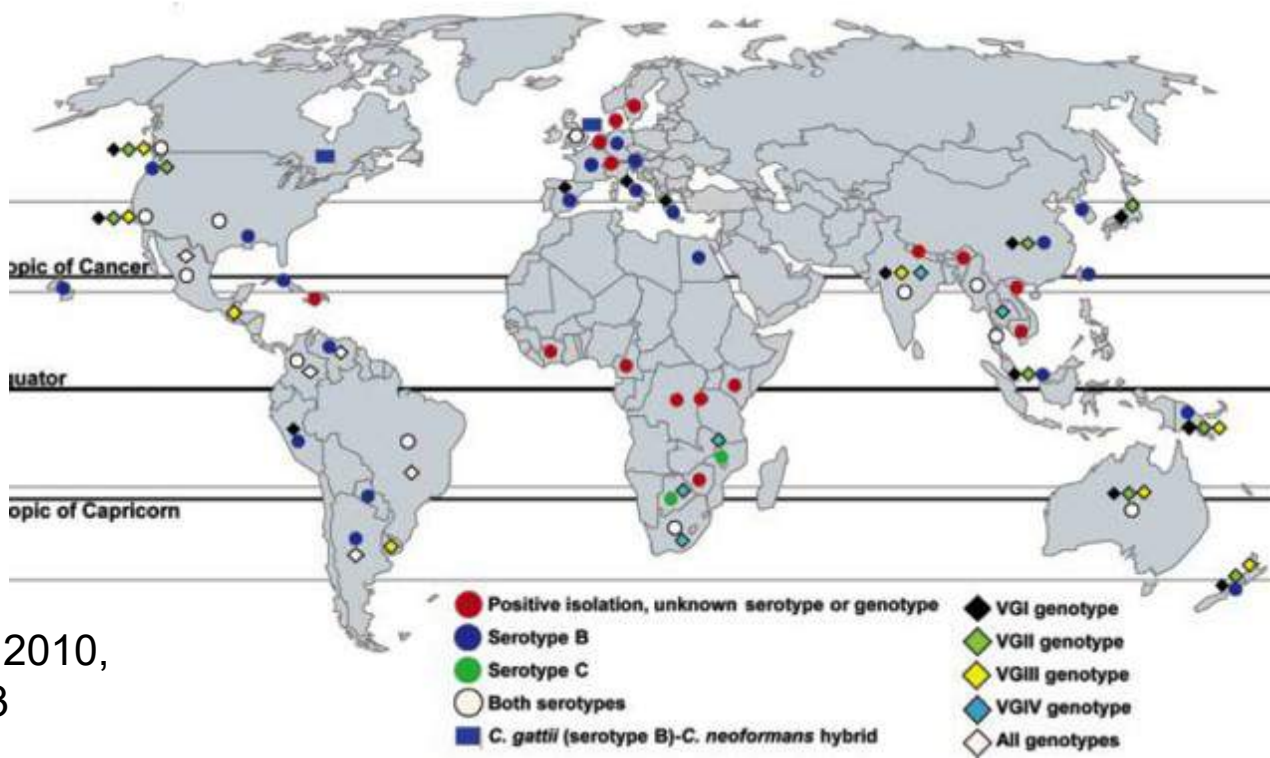
REACTIVATION?

MULTIPLE INF?

Cryptococcus gattii

- ✓ Ecology: 50 tropical trees (eucalyptus), subtropical, temperate
- Emerging in HIV-infected patients in Africa
- Outbreak:
  - Since 1999: Vancouver Island, Canada (99-2007: 218 cases)
  - Since 2005: Oregon

Present in:
-Australia, New Zealand+++
-South Am, Africa, Japan, Europe:
-Autochtonous in France (Guyana)
-Spain, Greece, Italy



Springer,EID 2010, Galanis, EID, 2010, Harris CID 2011, Hagen EID 2013

Cryptococcus gattii: clinical presentation

- US
- 50% ID patients
- Mortality: 33%
- Risk factors for death:
  - Steroids
  - Lack of neurological

Clinical findings	
Pneumonia	31/57 (54)
Meningitis	29/59 (49)
Cryptococcoma: lung	20/61 (33)
Cryptococcoma: brain	6/24 (25)

Harris JR, CID 2011

- Canada
- 38% patients ID
- Mortality: 8.7%
- Risk factors for death:
  - Age
  - Neurological signs
- Clinical presentation:
  - Respiratory signs: 76.6%

Galanis, EID 2010

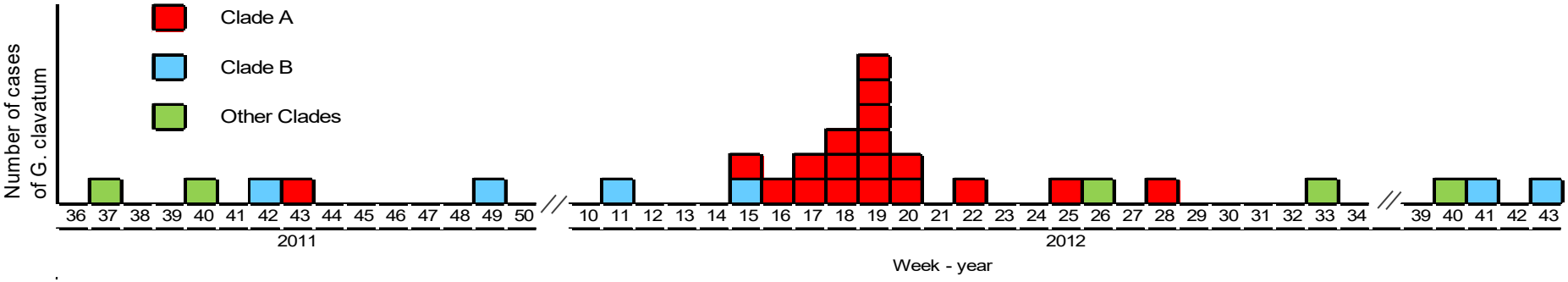
Respiratory signs after return from an endemic area

Characteristics of *C. gattii* genotypes

	VGI	VGII (VGIIa ++)	VGIII	VGIV
Main clinical presentation	CNS disease	Lung disease	CNS disease	CNS disease
Host	Immunocompetent	Both	Immunocompetent	Immunocompromised
Fluconazole MICs (vs *C. neoformans*)	comparable	higher	comparable	comparable
Frequency	34%	47% (All VGII genotypes)	11%	8%
Predominant zone of distribution	Australasia, Asia, Europe, USA	America (Clonal) Australia (Non clonal)	South America	Africa
Outbreak strain	Sporadic cases in USA	British Columbia, Pacific Northwest	Sporadic cases in USA	none

Guery et al. In press 2015

Multicenter outbreak of infections by *Saprochaete clavata* September 2011 – October 2012 (n = 30)



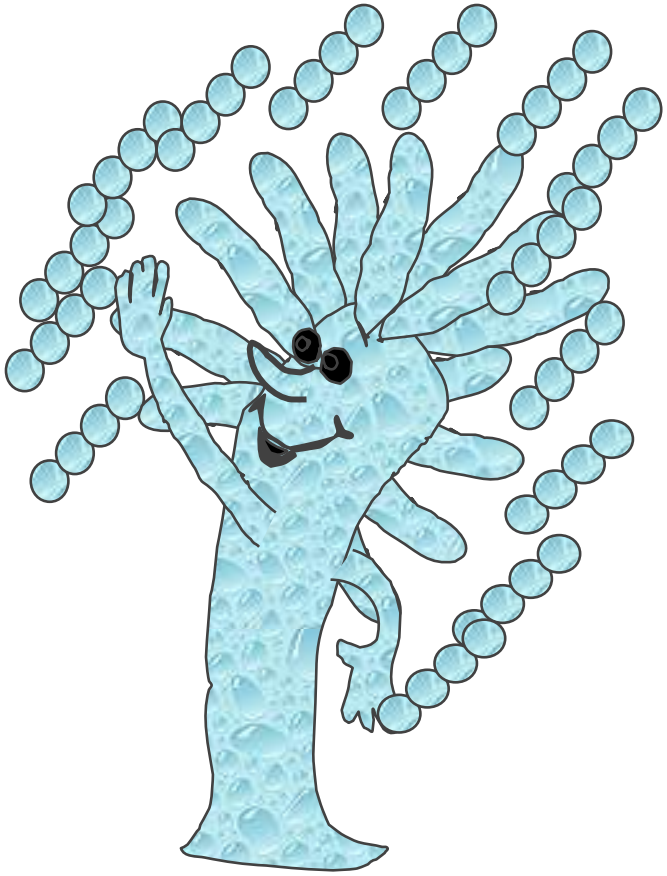
- 26 fungemias, 22 deaths at M1
- 16/18 outbreak cases belonged to clade A
- Eighteen cases within 8 weeks; 10 healthcare centers
- Several clade A cases (including GI tract colonization) since January 2015
- Source?

Clade characterization

- Whole-genome sequencing (Illumina)
- Clone-specific genotyping

Vaux Mbio 2014

Molds



Risk factors for mold infections

Exogenous
Inhalation / skin trauma

+++

Acute leukemia

Allo HSCT

HIV

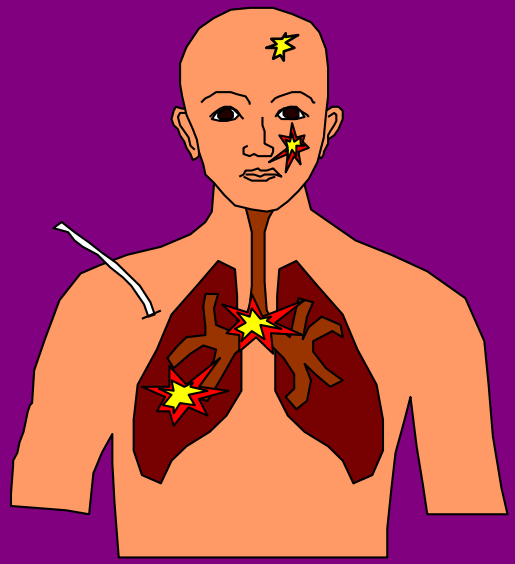
???

PID in children

SOT

ICU

Burned pts



Community

Healthcare

Travel

23–60% death at 3 months

IFI complicating new biotherapies in hematology

- **Ibrutinib** (BTK inhibitor):
  - Phase1 CNS lymphoma 7/18 IA; IA with steroids, PjP cases, cryptococcosis
- **Idelalisib** (PI3 kinase inhibitor):
  - PjP = primary prophylaxis
- Ruxolitinib (JAK 2 inhibitor)
- Venetoclax (BCL2 inhibitor)
- mTOR inhibitors
- Brentuximab (CD30 Ab)
- Blinatumomab (CD3-CD19 Ab)

NO SIGNAL OF IFI

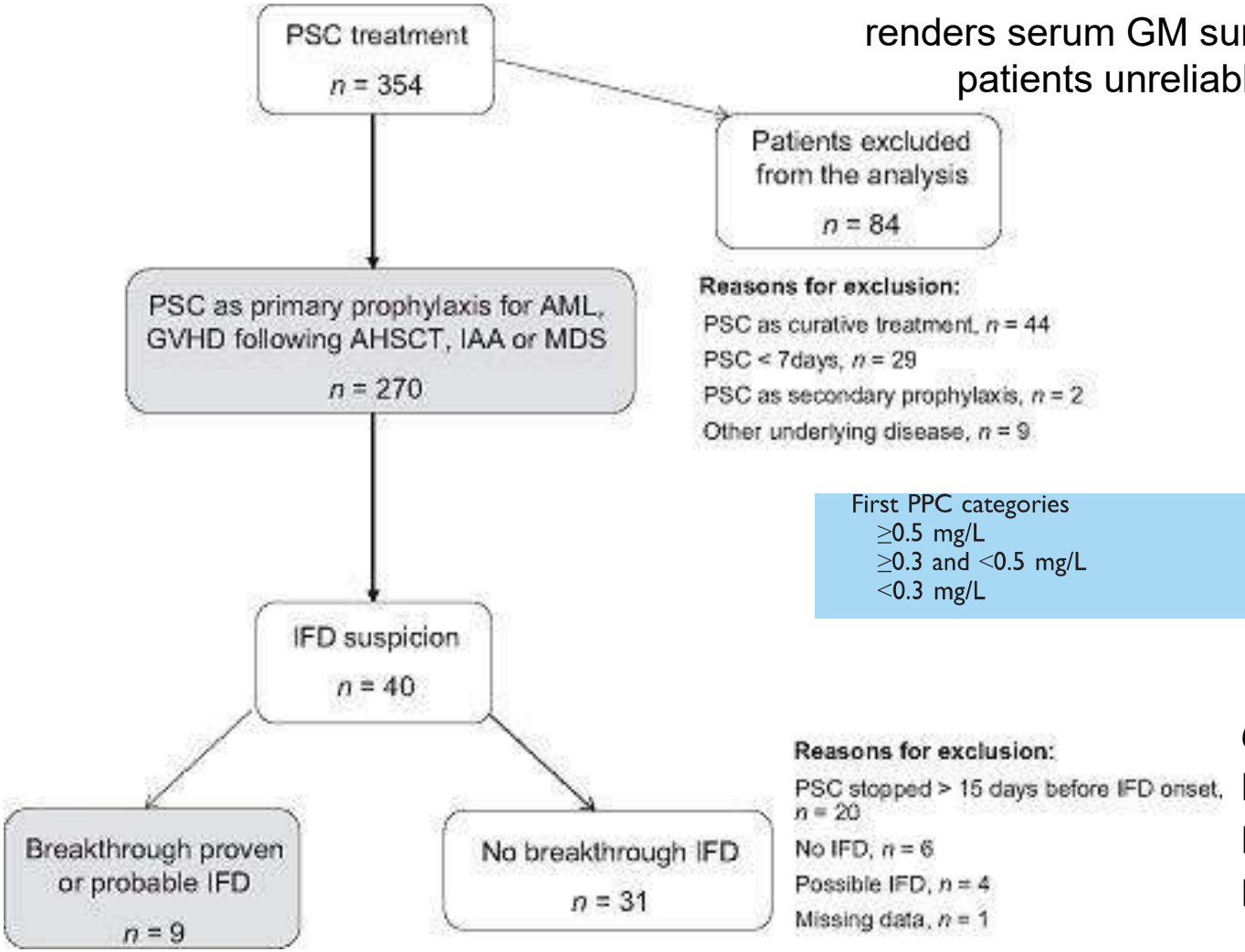
Literature review: ongoing

International Guidelines on antifungal prophylaxis in AML and allo-HSCT

		FLUCO	VORICO	ITRA	POSA	CASPO	L-AmB
ECIL-3	CT	C-I	-	C-I	A-I	-	C-I
	allo HSCT	A-I	A-I	B-I	A-I	-	C-I
German	neutropeni	C-I	C-II	C-I	A-I	C-I	C-II
	allo HSCT	A-I	C-II	C-I	A-I	-	-
IDSA		-	-	B-I	A-I	-	-
British		-	-	A-I	A-I	-	-
NCCN	AML-MDS	-	2B	-	1	-	2B
	allo HSCT	-	2B	-	1	2B	2B

Breakthrough invasive fungal disease in patients receiving posaconazole primary prophylaxis

« The low pretest risk of invasive aspergillosis in the context of effective antimold prophylaxis renders serum GM surveillance of asymptomatic patients unreliable » Duarte CID 2014

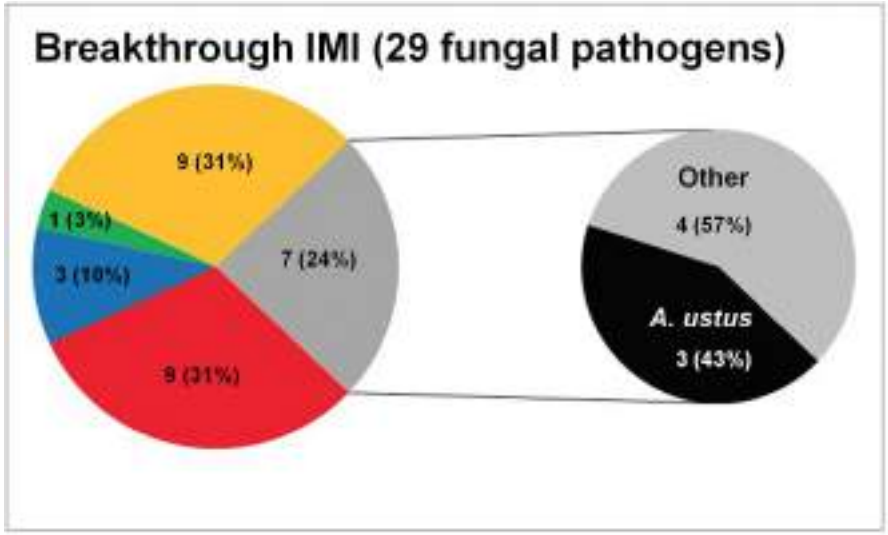


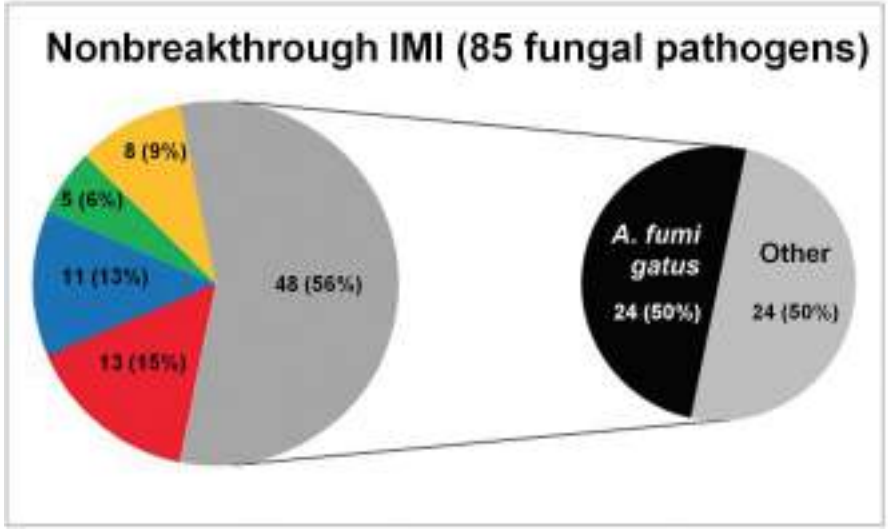
First PPC categories		
≥0.5 mg/L	1	(Reference)
≥0.3 and <0.5 mg/L	3.80 (0.54–27.0)	0.18
<0.3 mg/L	7.90 (1.32–47.3)	0.024

C.glabrata fungemia n = 2
IPA n = 3
Fusariosis n = 2
Mucormycosis n = 2

Lerolle, *CMI* 2014

Invasive mold infections following azole prophylaxis





Aspergillus spp.

Mucorales

Fusarium spp.

Scedosporium apiospermum complex

Other molds

Duke, 2004-2013
24 breakthrough IMI
Duration prophylaxis: 51d
73% appropriate through levels
83% intrinsic resistance of mold

Lamoth, CID 2017

Management issues in breakthrough fungal infections

Diagnostic work-up of patients under antifungal cover

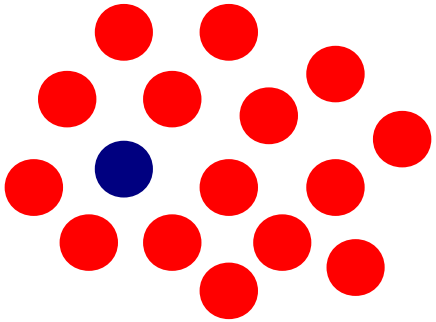
Resistance in fungi

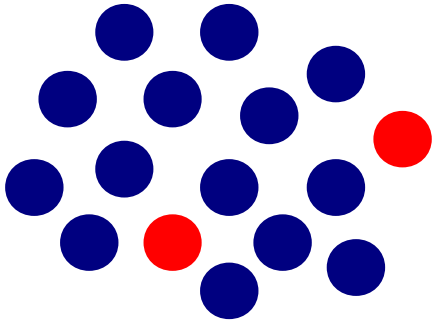
Resistant isolate

Susceptible isolate

Intrinsic resistance +++

Acquired resistance





« Low process »
No horizontal transmission

Resistant species

Susceptible species

1. Appropriate identification at the species level +++

2. ATF: Most often selection of species with higher MIC values

Triazole resistant *Aspergillus* spp.

- How to get a resistant infection
  - "Primary" resistance in antifungal naïve patients
    - Intrinsically resistant species
    - Isolate with acquired resistance (environment)
  - "Acquired" resistance in the AF-treated patient
    - Long-term treatment in the individual patient (chronic infection)

Aspergillus section *Fumigati*

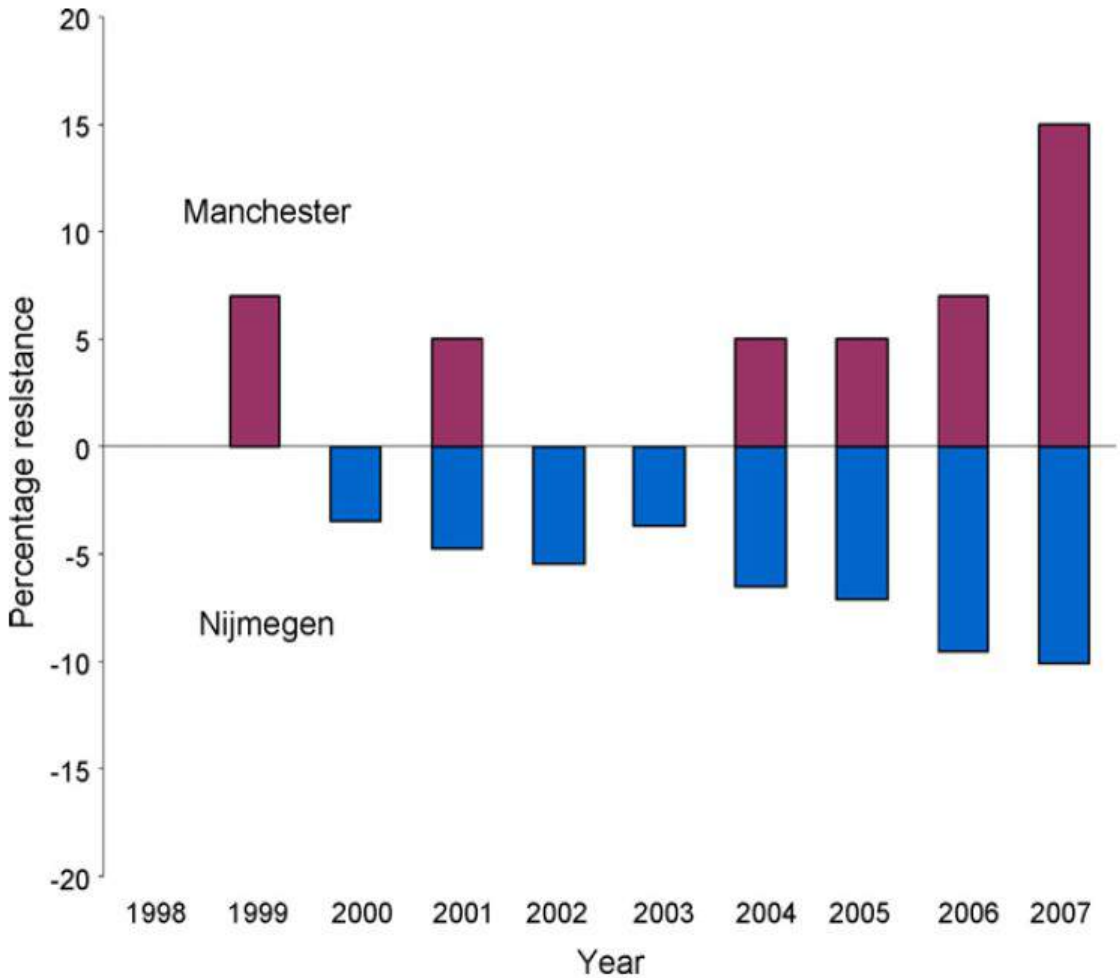
- 10 anamorphs
  - *A. brevipes*
  - *A. duricaulis*
  - *A. fumigatiaffinis* *
  - *A. fumigatus*
  - *A. fummisynnematus*
  - *A. lentulus* *
  - *A. novofumigatus*
  - *A. turcosus*
  - *A. unilateralis*
  - *A. viridinutans* *

- 23 telemorphs (*Neosartorya)*
  - *N. assulata*
  - *N. aurata*
  - *N. aureola*
  - *N. australensis*
  - *N. coreana*
  - *N. denticulata*
  - *N. ferenczii*
  - *N. fennelliae*
  - ***N. fischeri***
  - *N. galapagensis*
  - *N. glabra*
  - ***N. hiratsukae***
  - *N. laciniosa*
  - *N. mulplicata*
  - *N. papuensis*
  - ***N. pseudofischeri*** *
  - *N. quadricincta*
  - *N. spinosa*
  - *N. stramenia*
  - *N. spathulata*
  - *N. tatenoi*
  - ***N. udagawae***
  - *N. warcupii*

Isolates in red have been isolated from humans, * resistant to one or more AFs

Samson in "*Aspergillus fumigatus* and Aspergillosis" 2008; courtesy of M Arendrup

Azole-resistance in *A. fumigatus*



Manchester

Numerous different resistance mechanisms

Nijmegen

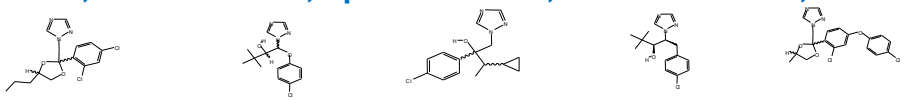
One mechanism responsible for >94% R

(TR34/L98H)

Verweij, *Drug Resist Updates* 2009; Howard, *Emerg Infect Dis* 2009

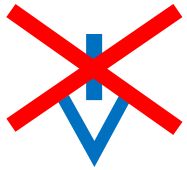
The environmental route

ropiconazole; tebuconazole; epoxiconazole; difenoconazole; bromuconazole



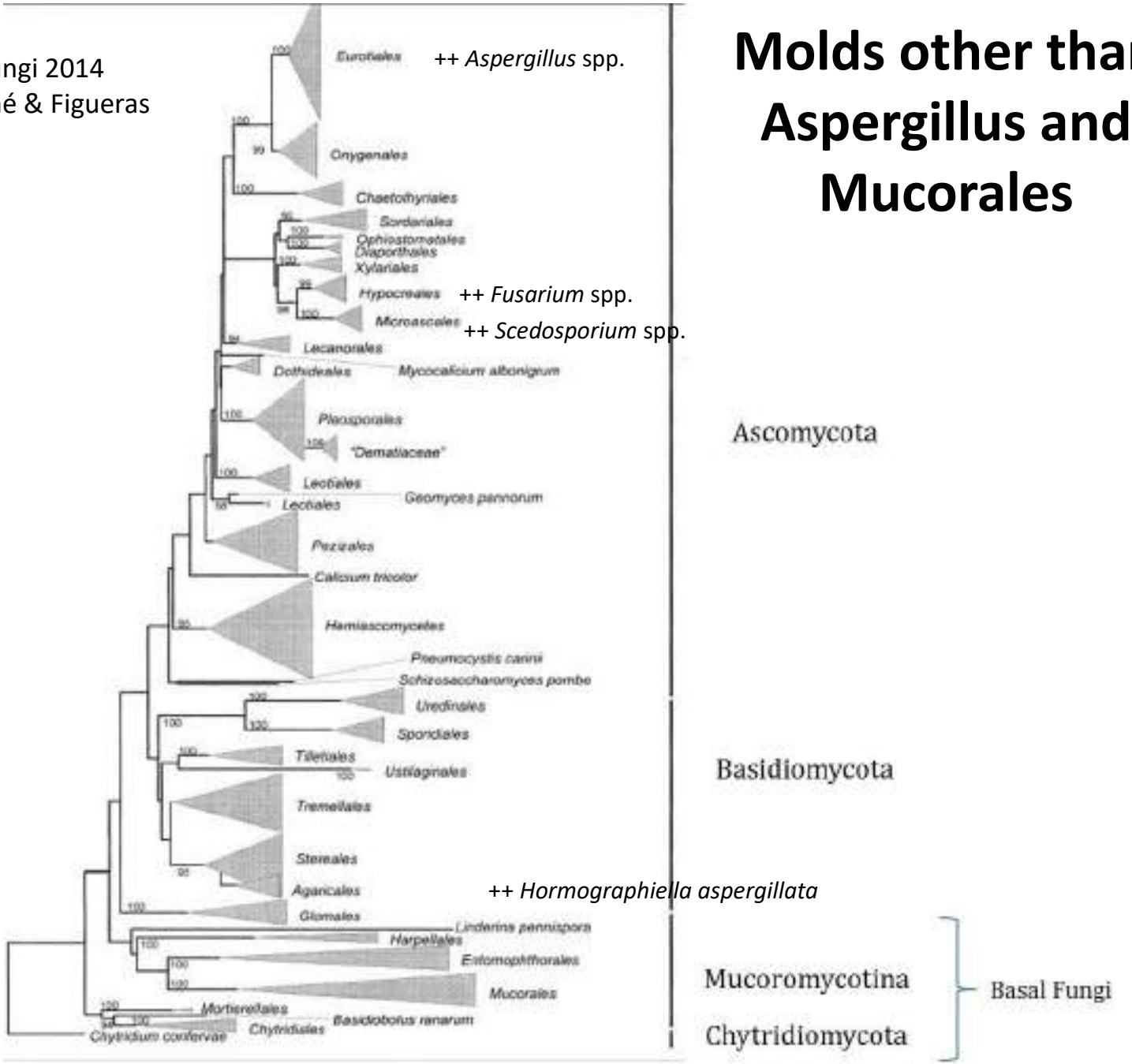
TR34/L98H
TR53
TR46/Y121F/T289A
G54?

Medical azoles



From :
Atlas of Clinical Fungi 2014
De Hoog, Guarro, Gené & Figueras

Molds other than Aspergillus and Mucorales



Incidence of various mold infections in allo-HSCT

Study (years)	Patients (n)	Aspergillosis		Zygomycosis		A/Z ratio	Fusariosis		Scedosporiosis	
		n	*Incidence (%)*	*n*	*Incidence (%)*		*n*	*Incidence (%)*	*n*	*Incidence (%)*
Allo-HSCT										
Baddley *et al.* (1997–1998)	94	12	12.8	1	1.1	12/1			1	1.1
Marr *et al.* (1985–1999)	5589	375	6.7	29	0.5	13/1	31	0.6	10	0.2
Martino *et al.* (1996–2000)	395	32	8.1	3	0.8	11/1	1	0.3	0	
Fukuda *et al.* (1997–2001)	163	22	13.5	4	2.5	5.5/1	1	0.6	0	
Kontoyiannis *et al.* (2002–2004)	n.r.	54		27		2/1	17		1	
Pagano *et al.* (1999–2003)	1249	79	6.3	1	0.1	79/1	3	0.2	1	0.1
Garcia-Vidal *et al.* (1998–2002)	1248	142	11.4	5	0.4	28/1	6	0.5	1	0.1
Neofytos *et al.* (2004–2007)	n.r.	99		12		8/1	4		0	
Kontoyiannis *et al.*† (2001–2006)	16,200	425	2.6	77	0.5	5.5/1	31	0.2	n.r.	

Caira, Exp Rev Antiinfect Ther 2011

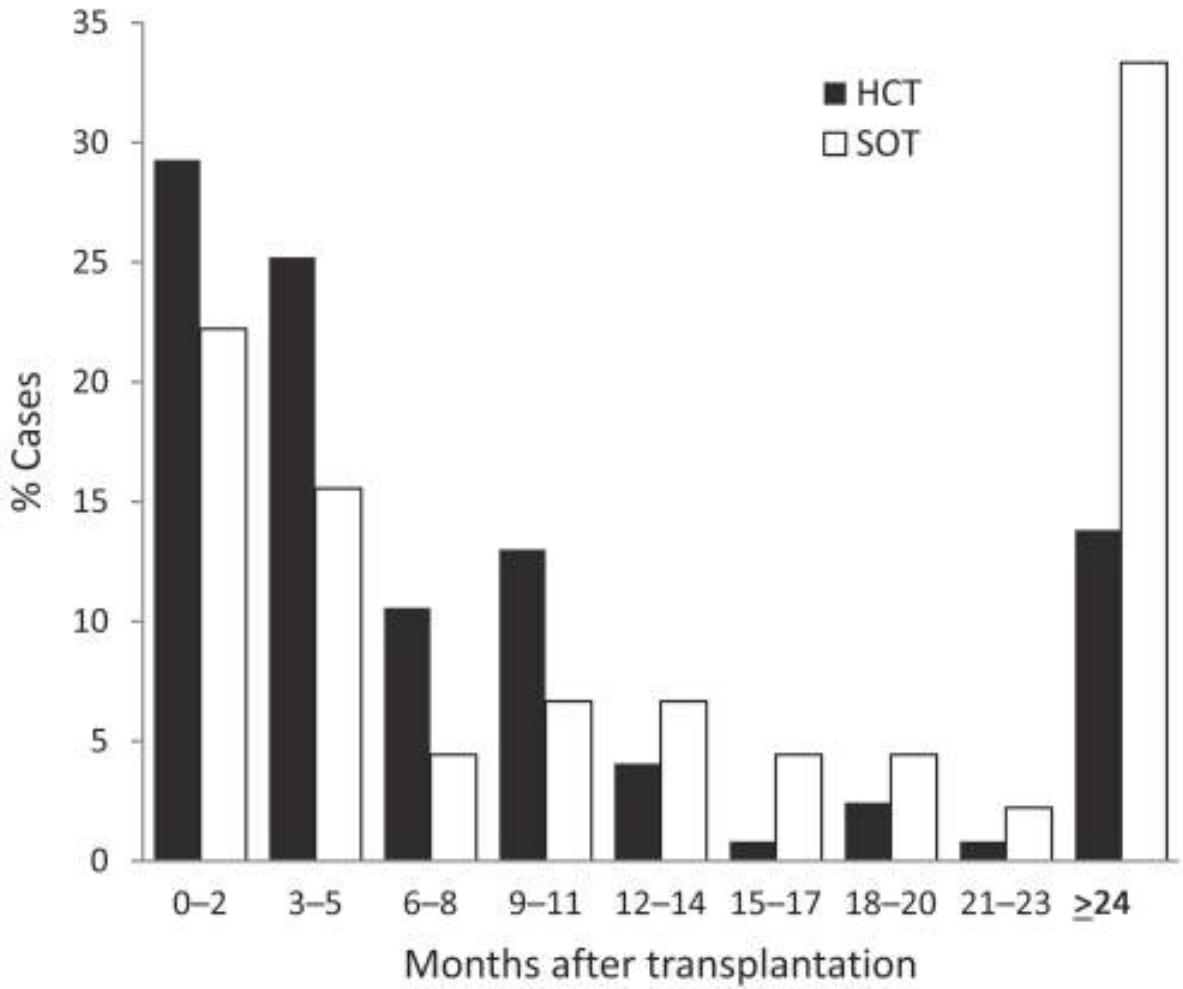
Variable epidemiology (region & hospital) of non-*Aspergillus* molds infections in transplant recipients in the USA

US region,† hospital code	No. transplant recipients		No. (%) cases			
	HCT	SOT	Mucorales, n = 105	*Fusarium* spp., n = 37	*Scedosporium* spp., n = 27	Total, N = 169
Northeast			7 (6.7)	3 (8.1)	2 (7.4)	12 (7.1)
A	608	1,532	5 (4.8)	1 (2.7)	1 (3.7)	7 (4.1)
B	245	377	1 (1.0)	2 (5.4)	1 (3.7)	4 (2.4)
C	1,107	NA	1 (1.0)	0	0	1 (0.6)
South			46 (43.8)	23 (62.2)	11 (40.7)	80 (47.3)
D	2,551	NA	18 (17.1)	12 (32.4)	1 (3.7)	31 (18.3)
E	646	549	6 (5.7)	3 (8.1)	6 (22.2)	15 (8.9)
F	363	NA	5 (4.8)	3 (8.1)	1 (3.7)	9 (5.3)
G	523	1,201	4 (3.8)	2 (5.4)	2 (7.4)	8 (4.7)
H	342	1,532	5 (4.8)	1 (2.7)	1 (3.7)	7 (4.1)
I	808	377	4 (3.8)	0	0	4 (2.4)
J	89	728	3 (2.9)	0	0	3 (1.8)
K	2,040	239	1 (1.0)	1 (2.7)	0	2 (1.2)
L	110	1,210	0	1 (2.7)	0	1 (0.6)
M	449	NA	0	0	0	0
N	511	NA	0	0	0	0
Midwest			35 (33.3)	9 (24.3)	7 (25.9)	51 (30.2)
O	970	2,111	8 (7.6)	5 (13.5)	4 (14.8)	17 (10.1)
P	1,028	1,391	8 (7.6)	2 (5.4)	0	10 (5.9)
Q	361	1,210	8 (7.6)	0	0	8 (4.7)
R	315	2,111	5 (4.8)	0	3 (11.1)	8 (4.7)
S	546	755	6 (5.7)	2 (5.4)	0	8 (4.7)
West			17 (16.2)	2 (5.4)	7 (25.9)	26 (15.4)
T	1,512	NA	9 (8.6)	2 (5.4)	4 (14.8)	15 (8.9)
U	854	NA	8 (7.6)	0	3 (11.1)	11 (6.5)
V	1,019	NA	0	0	0	0

Transnet. 23 centers. 2001-2006

Park EID 2011

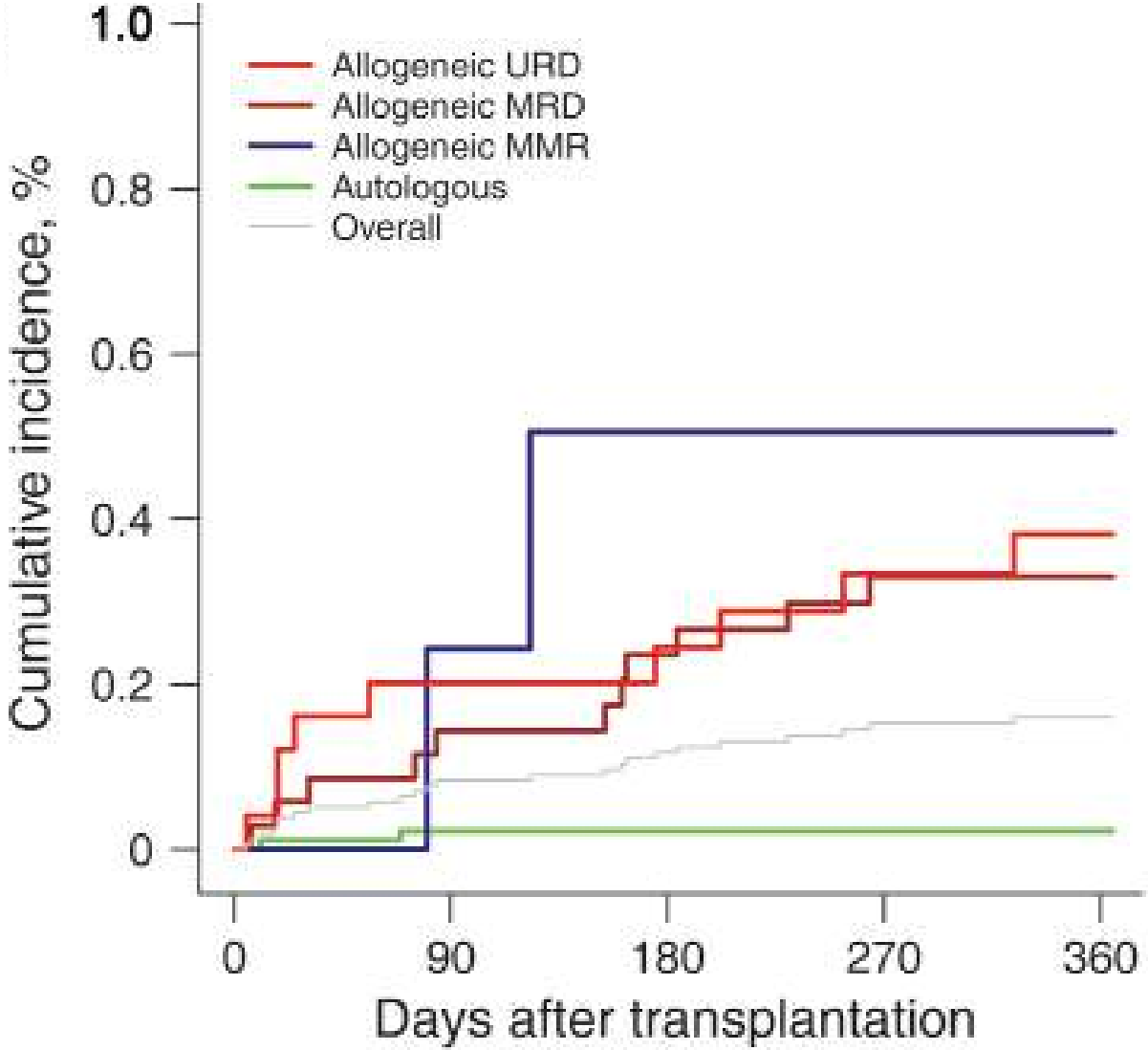
Time for occurrence of non-*Aspergillus* mold infections in transplant recipients



Transnet, 23 centers, 2001-2006

Park EID 2011

Cumulative incidence of fusariosis and scedosporiosis according to donor in HCT



Transnet. 23 centers. 2001-2006

Park EID 2011

Management of mucormycosis in hematology

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

547 cases
Incidence: 0.9/106/year
0.7 case/106 in 1997
1.2 case/106 in 2006

BEH, 2013

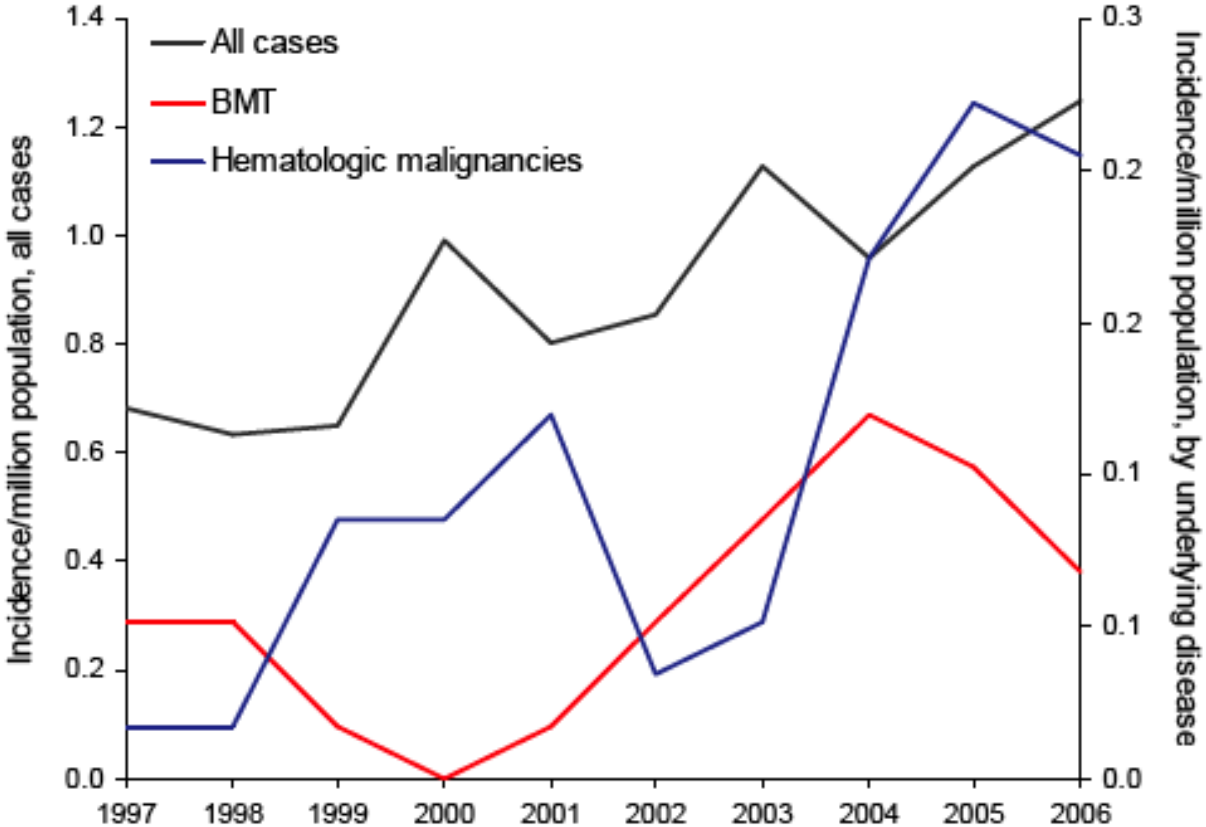


Figure 1. Evolution of the incidence of zygomycosis, France, 1997–2006. BMT, bone marrow transplantation.

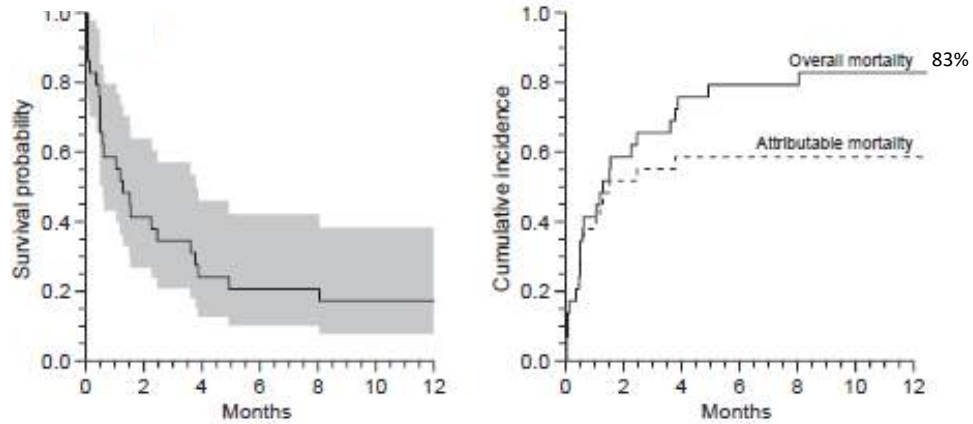
Emerg Infect Dis Sept 2009

Mucormycosis in Organ and Stem Cell Transplant Recipients

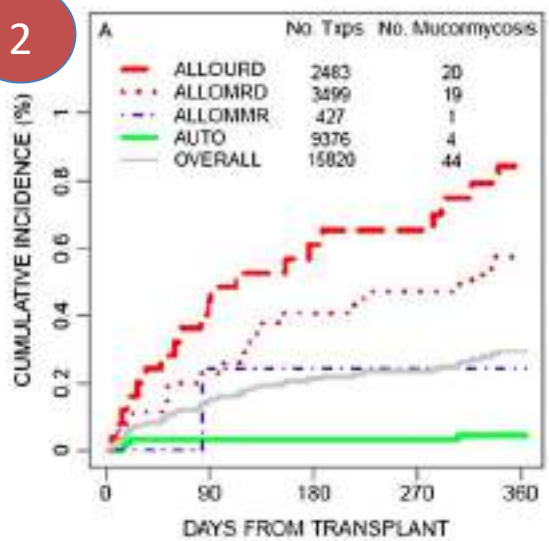
Clinical Infectious Diseases 2012
INVITED ARTICLE IMMUNOCOMPROMISED HOSTS

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]

- 2003–2008, allo HSCT France1
  - Mucormycosis prevalence: 0.4% (N=29)
  - 225 days after allo 0–2693
  - 23 breakthrough infections
  - 10 prior post-transplant infection
  - 89% patients corticosteroids 1 mg/kg



2



3 Transnet

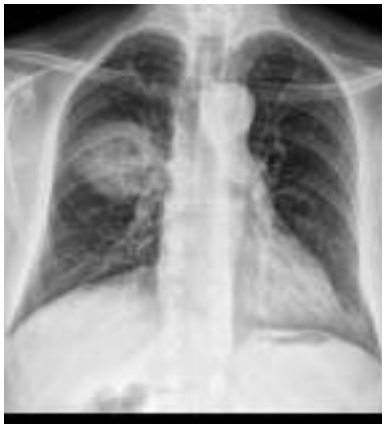
8% **43%**

63% of non-*Aspergillus* mold infections in transplant patients

1. Xhaard *Clin Microbiol Infect* 2012; 2. Park *Emerg Infect Dis 2011*; 3. Kontoyiannis *Clin Infect Dis* 2010.

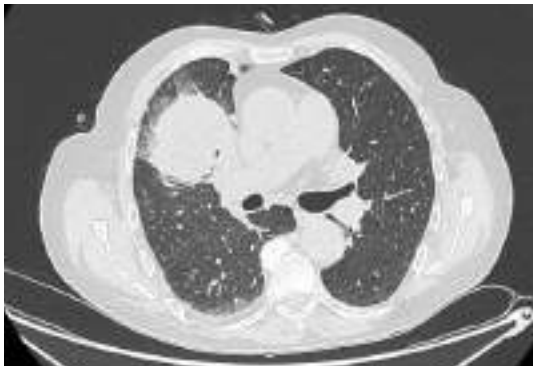
Pulmonary mucormycosis

- Associated with hematological malignancy



- Primitive, dissemination

- Symptomes, non specific
  - Fever, pain, hemoptysis
  - Lung inflitrate
  - Halo possible
  - Necrosis :
    - Extension
    - Vessels: bleeding– Dissemination



+

Mucormycoses pulmonaires

	Tedder et al (1994)[34]	Lee et al (1999)[32]	Chamilos et al (2005)[31]	Lewis (2014)[18]	Legouge et al (2014)[20]
Period	1948–1991	1970–1999	2002–2004	2000–2012	2003–2012
Countries	Single U.S. center + review	Review	Single U.S. center	Single U.S. center	Single French center
Nb of cases	30 + 255	87	16	75	16
Ratio F/M	1:2.3	1:3	1:1.3	1:2	1:2
Age, y	41 ± 21	44 (2–83)	48 (21–73)	57 (16–76)	60 (32–74)
Population	Global	Global	Hematological	Hematological	Acute leukemia
Underlying disease[a]					
HM	37%	32%	94%	100%	100%
Active HM	NA	NA	50%	57%	56%
Acute leukemia	26%	20%	44%	40%[c]	100%
HSCT	1%	11%	56%	39%	NA
Severe GVHD	NA	NA	44%	25%	NA
Neutropenia	NA	15%	19%/56%[b]	37%	94%
DM	32%	56%	50%	31%	0
SOT	7%	11%	0	0	0
Renal failure	18%	13%	0	0	0
Symptoms[a]					
Fever	38%	64%	63%	NA	87%
Dyspnea	19%	29%	38%		NA
Cough	50%	61%	19%		37%
Thoracic pain	26%	37%	13%		81%
Hemoptysis	16%	26%	13%		31%

Danion et al, Semin Resp Dis 2015

+

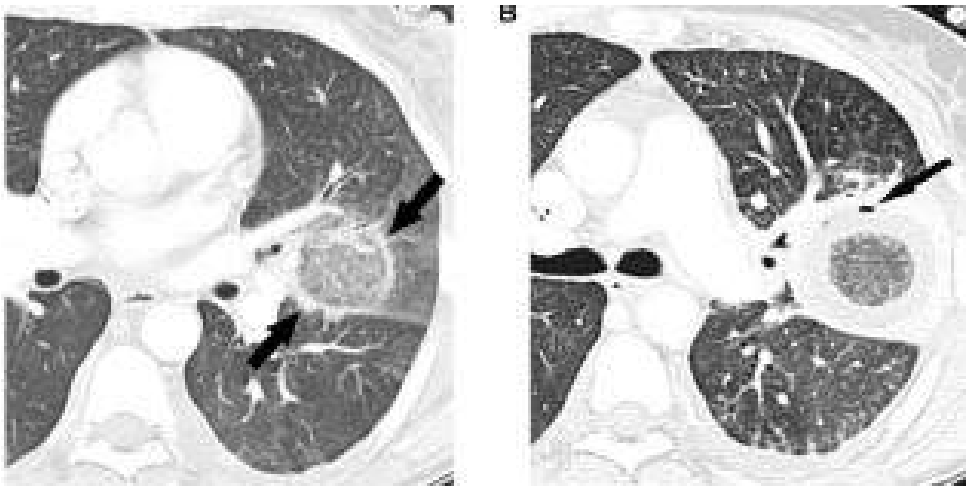
	Tedder et al (1994)[34]	Lee et al (1999)[32]	Chamilos et al (2005)[31]	Lewis (2014)[18]	Legouge et al (2014)[20]
Period	1948–1991	1970–1999	2002–2004	2000–2012	2003–2012
Countries	Single U.S. center + review	Review	Single U.S. center	Single U.S. center	Single French center
Nb of cases	30 + 255	87	16	75	16
CT scan					
Nodules	NA	NA	79%	80%	NA
Nb of nodules >10			64%	31%	NA
Micronodules			55%	NA	6%
Mass >3 cm			31%	NA	88%
Cavitation			25%	NA	0%
RHS			NA	NA	94%
Pleural effusion			63%	36%	12%
Time from onset of symptoms to CT			5 days [2–19]	NA	1 day [0–6][d]
Mucorales					
Rhizopus spp.	NA	41%	56%	48%	19%
Mucor spp.		27%	12%	22%	12%
Rhizomucor spp.		0	NA	0	50%
Cunninghamella spp.		21%	NA	13%	0
Lichtheimia spp.		0	NA	0	19%
Surgery	39%[e]	34%	NA	37%	37.5%
Mortality	80%[f]	56%	NA	37%	75%[g]
Mortality without surgery	68%	55%	NA	No difference[h]	60%[i]
Mortality with surgery	11%	27%	NA	No difference[h]	0%[i]

Danion et al, Semin Resp Dis 2015

Reverse halo sign

- IFI (n=189)

- 7 reverse halo sign (4%)
  - 1/132 aspergillosis
  - 6/ 37 mucormycosis (19%)



Wahba H, CID 2008

Reverse halo sign

- Single center experience
- Acute leukemia

Table 3. Evolution of Computed Tomographic Scans of 16 Patients With Proven Pulmonary Mucormycosis

CT characteristics	Days 0–5	Days 6–14	Days 15–26
No. of patients with CT performed	16/16 (100)	11/16 (69)	11/16 (69)
No. of CTs performed	25	14	11
No. of patients with CT during neutropenia	15/16 (94)	9/11 (82)	4/11 (36)
Typical RHS	15/16 (94)	7/11 (64)	0/11 (0)
Diameter of lesion ≤3 cm	2/16 (12)	0/11 (0)	1/11 (9)
Diameter of lesion >5 cm	7/16 (44)	8/11 (73)	9/11 (82)
Micronodules	1/16 (6)	7/11 (64)	10/11 (91)
Pleural effusion	2/16 (12)	6/11 (55)	7/11 (64)
Air-crescent sign or cavitation	0/16 (0)	1/11 (9)	4/11 (36)

Data are presented as No. of scans with characteristic/No. of scans with available data (%). Day 0 corresponds to the day of the first CT scan. Micronodules are defined by diameter <1 cm.

Abbreviations: CT, computed tomography; RHS, reversed halo sign.

Legouge, CID, 2014

+ Chirurgie et mucormycose pulmonaire

Etude monocentrique, 92% LA

	Emergency surgery (n = 27)	Elective surgery (n = 23)	All patients (n = 50)
Peri-operative data			
Median time (d) between IFI and surgery (range)	7 (2-41) *	35 (4-113) *	**15 (2-113)**
Unknown evaluation of haematological response before surgery	15 (56%) *	2 (9%) *	**17 (34%)**
Single fungal lesion on CT at time of surgery	9 (33%) *	17 (74%) *	**26 (52%)**
- in case of PM	5/5	6/7	**11/12 (92%)**
- in case of IPA or other IFI	4/22 *	11/16 *	**15/38 (39%)**
Persistent neutropenia (PMN<0.5G/l) at time of surgery	13 (48%) *	2 (9%) *	**15 (30%)**
Platelets transfusions during operative procedure	21 (78%) *	6 (26%) *	**27 (54%)**
Surgical procedures			
Lobectomy	26 (96%) *	14 (61%) *	**40 (80%)**
Wedge resection or Segmentectomy	1 (4%) *	9 (31%) *	**10 (20%)**
Assisted video-thoracoscopy	0 (0%) *	5 (22%) *	**5 (10%)**
Post-operative data			
Patients requiring intensive care unit (ICU)	16 (59%) *	7 (30%) *	**23 (46%)**
- median time (d) in ICU (range)	1 (0.5-30)	1 (1-2)	**1 (0.5-30)**
Median time (d) to hospital discharge post surgery	11 (6-30) *	7 (1-20) *	**8 (1-30)**
Level of confidence of IFI diagnosis after surgery**			
Proven IPA	21 (78%)	15 (66%)	**36 (72%)**
Proven PM	5 (18%)	7 (30%)	**12 (24%)**
Proven IFI due to *T. longibrachiatum*	1 (4%)	-	**1 (2%)**
Probable IPA	-	1 (4%)	**1 (2%)**

Chretien, CMI 2016

ECIL-6

Recommendations for first-line treatment of mucormycosis

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

Tissot et al. Haematologica 2017

Recommendations for salvage and maintenance therapy of mucormycosis

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

Tissot et al. Haematologica 2017

Isavuconazole et mucormycose

	Vital study 1st line Isavuconazole N=21	AmBizygo study L AmB high dose N=33
Chirurgie	43%	71%
Response W4		31%
Partial response		13%
Complete response		19%
Décès		21%
Response W6	14%	
Partial response	0	
Complete response	14%	
Stable	43%	
Décès	33%	
Response W12	10%	48%
Partial response	5%	19%
Complete response	5%	29%

Management of disseminated fusariosis in Hematology

Fusarium spp. = 25% of non-*Aspergillus* molds in HSCT [Park, EID 2011]

Fusarium spp.

- Hyaline mould, septate, ubiquitous, soil, water, showers, water taps, air
- Toxins producer; plant

Fusariosis : better clinical suspicion = earlier diagnosis in hematology (n=84)

Fever	92%
Skin lesions	77% (multiple 66%)
Lung infiltrates 5,2 cm	54%
Sinusitis	36%
Dissemination	79%
Fungemia	55%

Poor prognostic factors :

Persistent neutropenia : HR = 5.43 [4% survival]

Corticosteroids : HR = 2.18 [30% survival]

No factor : 67% survival

Nucci Cancer 2003

Risk factors for fusariosis in 345 allo-HSCT recipients

Prospective cohort, 8 centers in Brazil; 15 fusariosis cases

	Early (Until Day 40)		Late (After Day 40)	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.01 (.98–1.04)	.54	1.05 (.98–1.12)	.12
Male sex	1.45 (.44–4.83)	.54	2.85 (.32–25.64)	.35
Center 7 vs other centers	5.15 (1.66–15.97)	.005	2.53 (.42–15.33)	.31
Acute myeloid leukemia	4.38 (1.39–13.81)	.01	5.13 (.85–30.82)	.07
HLA mismatched	1.95 (.41–9.17)	.40	0.22 (.01–14.68)	.48
Unrelated donor	2.36 (.67–8.37)	.18	0.03 (.01–46.34)	.49
Stem cell source: peripheral blood vs others	1.06 (.32–3.51)	.93	2.42 (.43–13.62)	.31
Nonmyeloablative conditioning regimen	0.46 (.12–1.72)	.25	35.08 (3.90–315.27)	.001
Previous IMD	2.86 (.37–22.17)	.31	10.65 (1.19–95.39)	.03
Receipt of ATG in the conditioning regimen	22.17 (4.85–101.34)	<.001	NA	NA
Duration of neutropenia until day 40	1.01 (.99–1.02)	.70	NA	NA
Room with HEPA filter	0.55 (.12–2.49)	.44	NA	NA
Receipt of corticosteroids until day 40	2.57 (.75–8.79)	.13	NA	NA
Acute GVHD until day 40	1.23 (.60–2.51)	.57	NA	NA
Hyperglycemia requiring insulin	5.17 (1.40–19.11)	.01	NA	NA
CMV reactivation until day 40	1.69 (.21–13.70)	.62	NA	NA
Receipt of corticosteroids after day 40	NA	NA	2.49 (.41–14.99)	.32
Neutropenia after day 40	NA	NA	1.66 (.19–14.88)	.65
Grade III/IV GVHD after day 40	NA	NA	16.50 (2.67–102.28)	.003
CMV reactivation after day 40	NA	NA	5.99 (1.00–35.84)	.05

Garnica, CID 2015

Galactomannan detection during invasive fusariosis

- 15/18 (83%) GM positive; Se 83%; Sp 67%

Patient	Primary source of diagnosis	Direct exam	Culture	Histopathology	Time (days) from procedure to diagnosis	Time (days) from 1st serum GMI to diagnosis
1	Skin	Positive	Positive	Positive	0	−16*
2	Skin	Positive	Positive	Positive	0	+4
3	Skin	Positive	Positive	Positive	0	−1
4	Skin	Positive	Positive	Positive	0	−13
5	Skin	Positive	Positive	Positive	0	−14
6	Skin	Positive	Positive	Positive	0	−8
7	Skin	Positive	Positive	Positive	0	−6
8	Skin	NP	Positive	Positive	8	Negative
9	Skin	Negative	Positive	Positive	5	+8
10	Skin	Negative	Negative	Positive	11	Negative
11	Blood	NA	Positive	NA	1	−25**
12	Blood	NA	Positive	NA	3	−3
13	Blood	NA	Positive	NA	4	−10
14	Blood	NA	Positive	NA	3	+2
15	Blood	NA	Positive	NA	3	+6
16	Sinus aspirate	Positive	Positive	NA	0	Negative
17	Synovial fluid	Negative	Positive	NA	4	−39***
18	Bronchoalveolar lavage	Positive	Positive	Positive (skin)	0	−10

Nucci, PLoS ONE 2014

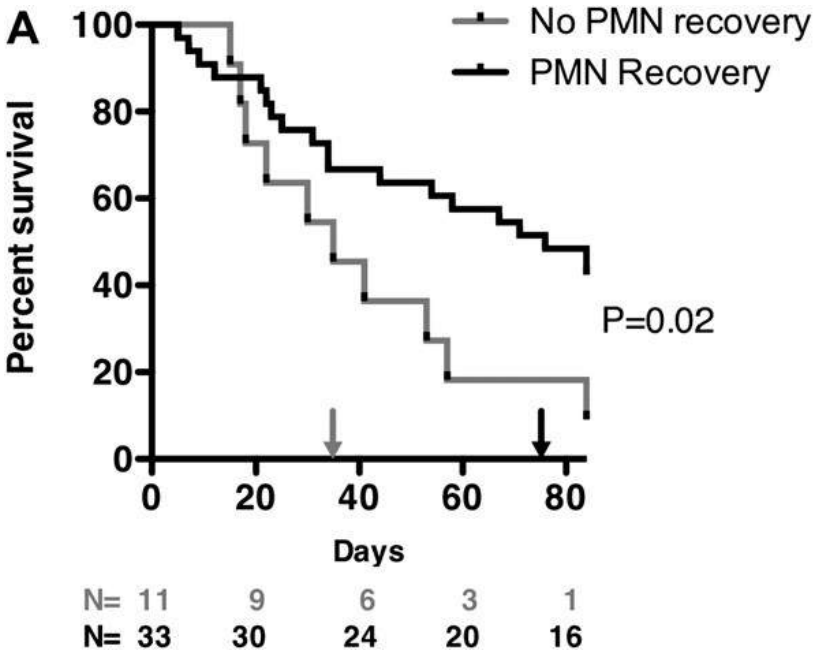
Outcome of fusariosis

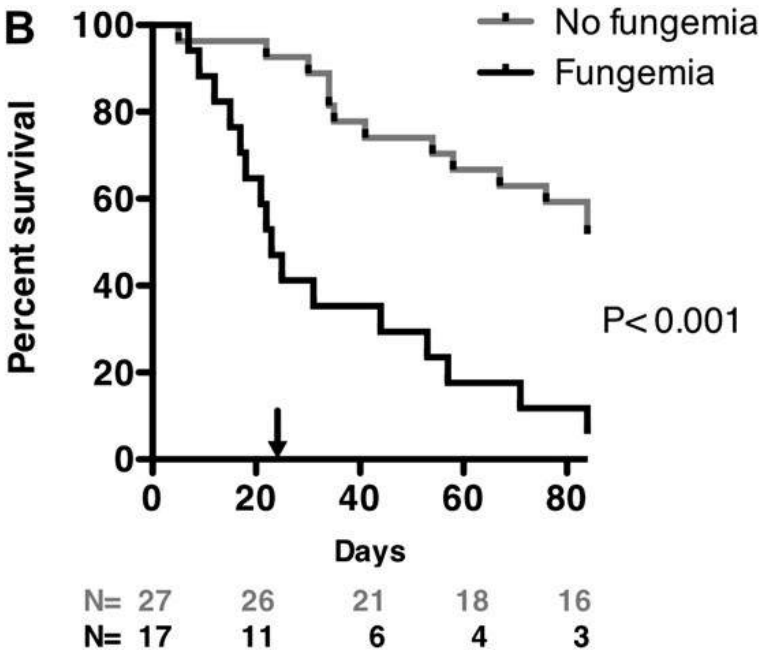
Fungemia: independent factor for death
[OR 15.9; 1.1-231, p = 0.042]

Study (years)	Drug in study	Cases (n)	Outcome, n (RR)
Case series			
Nucci *et al.* (n.r.)	Mixed	84	66 (79%)
Nucci *et al.* (1985–2001)	Mixed	54 allo-HSCT, 7 auto-HSCT (0.1%)	8 (13%)
Campo *et al.* (1998–2009)	Mixed	44	15 (34%)
Kontoyiannis *et al.* (2001–2006)	Mixed	31 allo-HSCT	2 (6%)
Hsiue *et al.* (2000–2008)	Mixed	12	7 (58%)
Lortholary *et al.* (1996–2002)	Voriconazole	73	30 (41%)
Total		305	128 (42%)
Clinical trials			
Walsh *et al.*† (1990–1995)	AmB lipid complex	11	9 (82%)
Perfect (1996–2000)	AmB lipid complex	26	12 (46%)
Raad *et al.*† (n.r.)	Posaconazole	21	10 (48%)
Perfect *et al.*† (n.r.)	Voriconazole	11	5 (45.5%)
Total		69	36 (52%)

Caira, Exp Rev Antiinfect Ther 2011

Outcome of fusariosis according to PMN recovery or fungemia





Campo, J Infect 2010

Outcome of fusariosis : underlying condition and site of infection

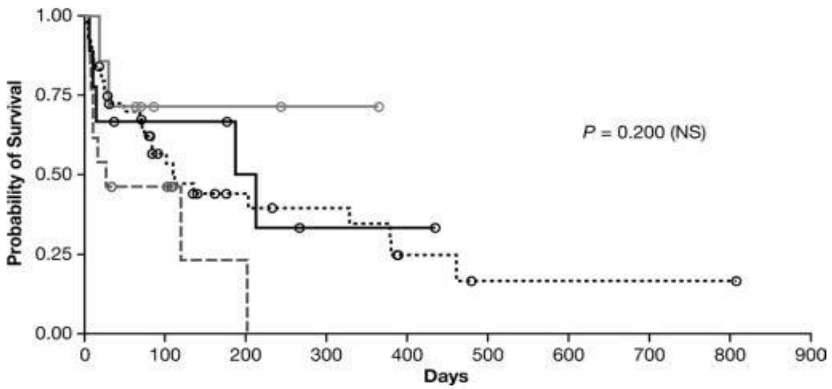


FIG. 1. Kaplan-Meier curves of patient survival, by underlying condition. Differences between groups were not significant ($P = 0.2$). Hematopoietic stem cell transplant, gray dashed line; hematologic condition, black dotted line; chronic immune suppression, solid black line; other underlying condition, solid gray line; censored patients, black or gray circles.

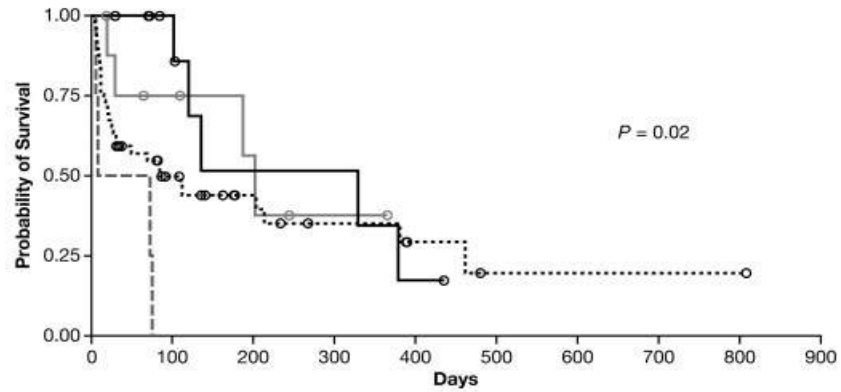


FIG. 2. Kaplan-Meier curves of patient survival, by site of infection. Differences between groups were significant ($P = 0.02$). Brain, gray dashed line; disseminated (excluding brain), black dotted line; lung/sinus, solid black line; other, solid gray line; censored patients, black or gray open circles.

- NS
  42% success rate
  Vori similar to combination
- Lung/sinus>Disseminated >Brain

Lortholary AAC 2010

Fusarium spp. : intrinsic « multiple resistance »

In vitro susceptibility of *Fusarium* species

	AMB	ITRA	VORI	POSA	CASPO	TERBI	MICA
Fusarium oxysporum complex	2/4	≥8/≥8	4/8	2/≥8	≥8/≥8	2/8	≥8/≥8
Gibberella fujikuroi complex (n=63)	4/8	≥8/≥8	4/8	4/≥8	≥8/≥8	1/2	≥8/≥8
Fusarium solani complex (n=143)	2/8	≥8/≥8	8/≥8	≥8/≥8	8/≥8	≥8/≥8	≥8/≥8
Fusarium dimerum complex (n=16)	0.5/0.5	≥8/≥8	2/8	≥8/≥8	8/≥8	0.5/2	≥8/≥8

- NRCMA, unpublished data

Fusariosis : principles of therapy

- Surgical removal of necrotic tissues (sinus, eye, skin, bone …)
- Removal of infected catheter
- Voriconazole = first line, 9/21 : 44% favorable response;
  - 3 months survival = 71%
- Ampho B lipid derivative

Kontoyiannis Leuk Lymphoma 2004; Perfect CID 2005; Perfect CID 2003

Voriconazole for the management of fusariosis

- Retrospective international study
- 73 pts (++2nd line)
  - Allogeneic SCT (18%)
  - Hem malignancy (60%)
  - Neutropenic = 64%
- Localization
  - Brain (5%)
  - Disseminated outside brain (67%)
- Lortholary AAC 2010

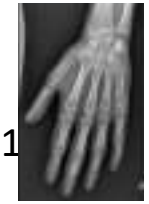
TABLE 4. Comparisons of outcomes for invasive fusariosis cases treated with voriconazole

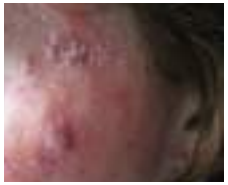
Comparison (statistical method)[a]	No. with clinical response/ total no. of patients (%)	*P* value
Male vs female (C)	21/48 (44) vs 13/25 (52)	NS[b]
Proven vs probable infection (C)	31/67 (46) vs 4/6 (67)	NS
Primary vs salvage/unknown therapy (C)	7/16 (44) vs 27/57 (47)	NS
Combination vs voriconazole alone/unknown (C)	6/13 (46) vs 28/60 (47)	NS
Voriconazole database vs NRCMA (C)	20/39 (51) vs 14/34 (41)	NS
Neutropenia (F)		≤0.03[c]
Recent	17/47 (36)	
None	5/7 (71)	
Status unknown	12/19 (63)	
Fusarium species (F)		NS
F. solani complex	9/16 (56)	
F. moniliforme complex	2/8 (25)	
F. proliferatum complex	4/8 (50)	
F. oxysporum complex	6/7 (86)	
All other *Fusarium* spp.	13/34 (38)	

[a] C, chi-square test; F, Fisher's exact test.
[b] NS, not significant.
[c] *P* value for outcome in patients with neutropenia versus patients without neutropenia or with neutropenia status unknown.

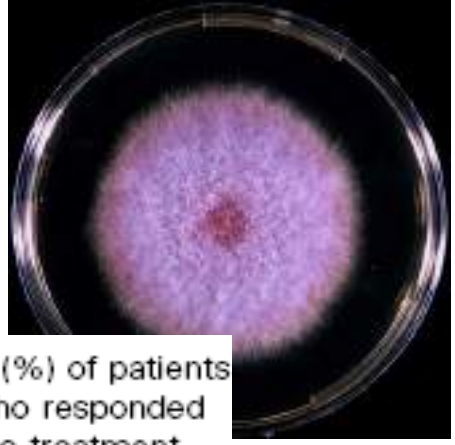
Voriconazole: important considerations

- **First-line therapy, but consider (according to geographical area) triazole resistant *A. fumigatus*** (van der Linden, CID 2013)
- **Oral therapy when possible (cost)**
- **Therapeutic drug monitoring: trough levels: >1 Pt< 5 μg/ml** (Park, CID 2012)
  - Efficacy and safety
- **Hepatic dysfunction**
  - Reduce dosage
- **Drug interactions**
  - Monitor immunosuppressive/other therapy
- **Metabolism**
  - Increased levels in patients likely to metabolize drug poorly (Asia, CYP-2C1 polymorphism)





Posaconazole as Salvage Treatment for Invasive Fusariosis in Patients with Underlying Hematologic Malignancy and Other Conditions



Issam I. Raad,[1] Ray Y. Hachem,[1] Raoul Herbrecht,[5] John R. Graybill,[2] Roberta Hare,[3] Gavin Corcoran,[4] and Dimitrios P. Kontoyiannis[1]

CID 2006

Characteristic	No. of patients	No. (%) of patients who responded to treatment
Fusarium species as the primary pathogen		
All patients	21	10 (48)
Patients with proven infection[a]	18	7 (39)
Patients with probable infection[a]	3	3 (100)
Age, years		
<18	3	1 (33)
18–64	14	6 (43)
≥65	4	3 (75)
Sex		
Female	13	7 (54)
Male	8	3 (38)
Neutropenia[b]	8	3 (38)
Risk factor[c]		
Hematologic malignancy	16	7 (44)
Nonhematologic malignancy (breast cancer)	2	0
Hematopoietic stem cell transplant	6	1 (17)
Allogeneic	4	1 (25)
Autologous	2	0
Solid organ transplant	2	2 (100)
Diabetes	6	3 (50)

Changing outcome during invasive fusariosis : impact of antifungal therapy

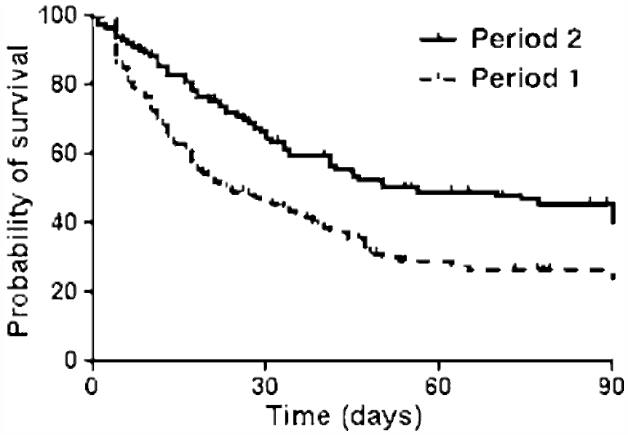


FIG. 1. Probability of 90-day survival of 233 patients with invasive fusariosis in period 1 (1985–2000) and period 2 (2001–2011).

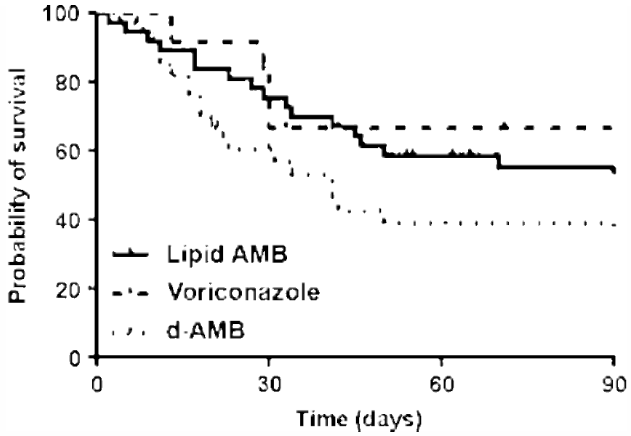


FIG. 2. Probability of 90-day survival of 83 patients with invasive fusariosis in period 2 treated with deoxycholate amphotericin B (d-AMB), voriconazole, or a lipid formulation of amphotericin B (Lipid AMB).

N = 206 cases

Factors associated with d90 death

	Unadjusted		Adjusted	
Variable	HR (95% CI)	p	HR (95% CI)	p
Haematological disease	5.70 (0.79–41.24)	0.08	5.26 (0.71–38.73	0.11
Receipt of corticosteroids	2.21 (1.24–3.94)	0.007	2.11 (1.18–3.76)	0.01
Neutropenia at end of treatment	2.61 (1.52–4.46)	<0.001	2.70 (1.57–4.65)	<0.001
Disseminated disease	1.72 (0.90–3.26)	0.09	1.45 (0.72–2.94)	0.30
Primary treatment with deoxycholate amphotericin B[a]	1.75 (1.02–3.01)	0.04	1.83 (1.06–3.16)	0.03
Primary treatment with voriconazole[a]	0.61 (0.34–1.11)	0.09	0.77 (0.38–1.55)	0.47

HR, hazard ratio.
[a]As a single agent. Neither lipid amphotericin B (HR 0.67, 95% CI 0.27–1.69) or combination therapy (HR 1.20, 95% CI 0.63–2.28) was significant by univariate analysis.

Nucci CMI 2014

IFSIG guidelines for first line treatment of fusariosis in immunodepressed patients

Intention	SoR	QoE	Comment
Voriconazole	A	II	TDM
LAmB	B	II	
ABLC	C	III	
AmBd	D	II	
Echinocandin	D	III	Resistant
Any combination	C	III	Limited reports Not better than voriconazole

Correction neutropénie

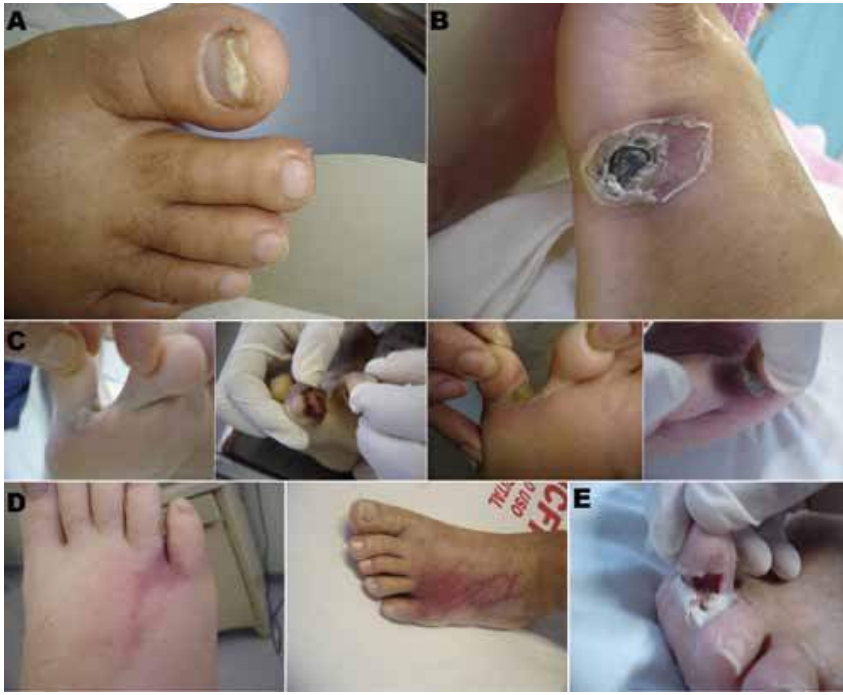
Réséquer les tissus infectés (sinus, œil, peau, os …)

Retrait d'un cathéter infecté

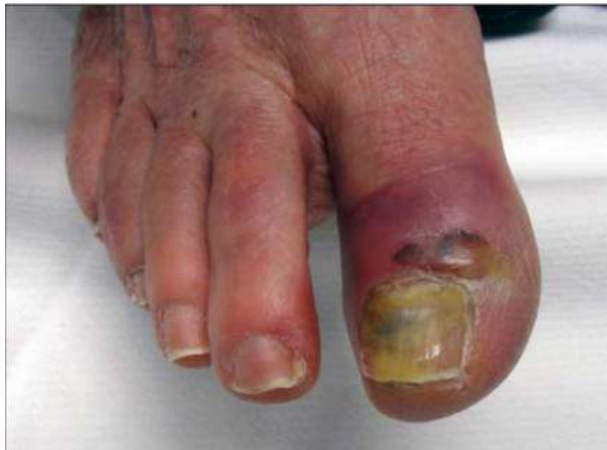
CMI, 2014

Preventive measures against fusariosis

- Skin integrity : avoid portal of entry
  - care of intertrigo, skin ulcer, nails
- Hygiene procedures:
  - air
  - water (57% (+)/283 samples (Anaissie CID 2001)



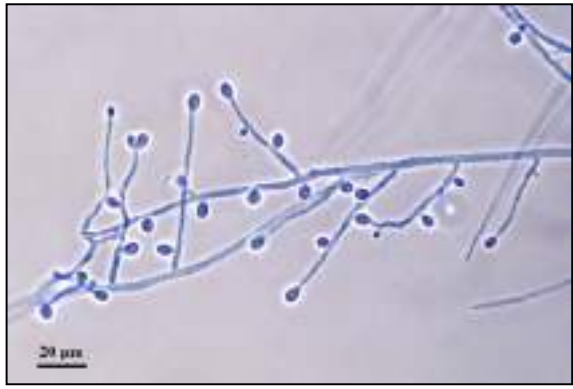
Nucci, EID 2013



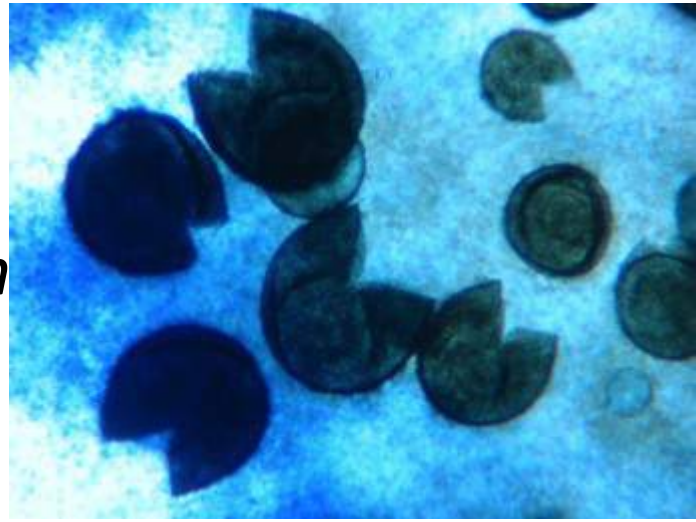
- Secondary prophylaxis
  - Reduce immunosuppression if feasible
  - Targeted therapy (voriconazole)

Management of disseminated scedosporiosis in Hematology

Scedosporium spp.

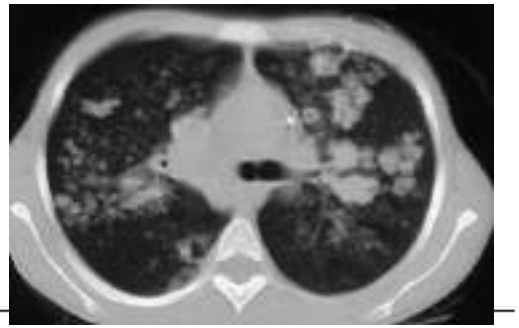


- Ubiquitous, septate molds
  - Soil, sewage water, potted plants
- *Scedosporium apiospermum com*
  - ***Scedosporium boydii***
  - ***S. aurantiacum***
  - ***S. minutisporum***



Infections Due to *Scedosporium apiospermum* and *Scedosporium prolificans* in Transplant Recipients: Clinical Characteristics and Impact of Antifungal Agent Therapy on Outcome

Clinical Infectious Diseases 2005; 40:89–99



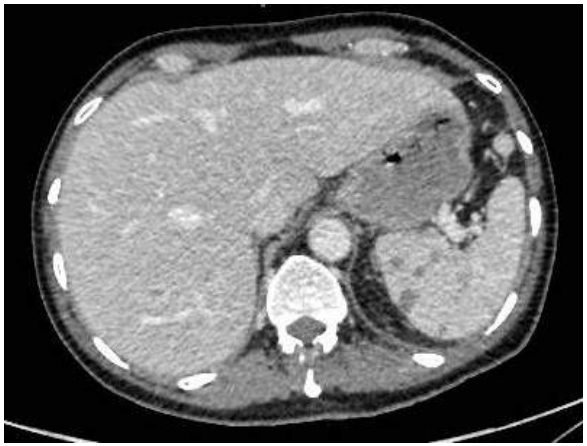
Shahid Husain,[1] Patricia Muñoz,[5] Graeme Forrest,[2] Barbara D. Alexander,[3] Jyoti Somani,[4] Kathleen Brennan,[2] Marilyn M. Wagener,[1] and Nina Singh[1]

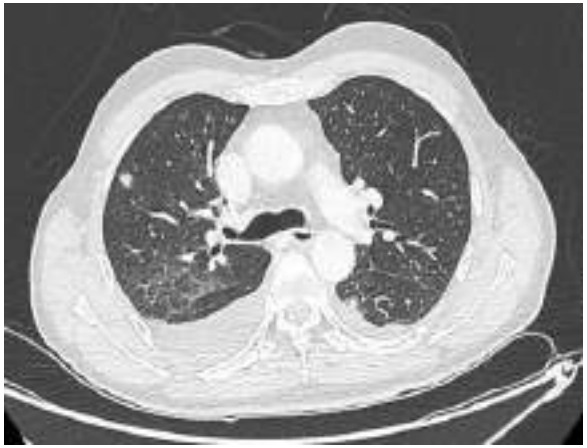
Variable	HIV-infected patients (n = 14)	Organ transplant recipients (n = 57)	Patients with hematologic malignancies (n = 69)	Other IS patients (n = 51)	IC patients (n = 56)
Age,[a] mean years	37	50	44	51	36
Prior receipt of antifungal prophylaxis[b]	46.0 (6/13)	20.0 (9/45)	34.0 (21/62)	4.0 (2/51)	0.0 (0/56)
Clinical presentation					
CNS involvement	15.4 (2/13)	25.0 (13/53)	28.0 (19/67)	22.0 (11/49)	17.0 (10/56)
Pulmonary involvement[b]	50.0 (7/14)	46.0 (24/52)	62.0 (41/66)	33.0 (16/49)	15.0 (8/53)
Skin involvement[c]	7.0 (1/14)	32.0 (17/53)	[illegible]	[illegible]	7.0 (4/56)
Fungemia[b]	23.0 (3/13)	16.0 (7/45)	[illegible]	[illegible]	[illegible] (2/26)
Disseminated infection[b]	57.0 (8/14)	55.0 (29/53)	[illegible]	[illegible]	[illegible] (11/55)
Species isolated					
Scedosporium apiospermum	71.0 (10/14)	83.0 (44/53)	[illegible]	[illegible]	[illegible] (35/56)
Scedosporium prolificans	28.6 (4/14)	17.0 (9/53)	[illegible]	[illegible]	37.5 (21/56)
Neutropenia[b]	39.0 (5/13)	13.0 (4/32)	[illegible]	[illegible] (2/45)	0.0 (0/54)
Renal failure[b]	0.0 (0/4)	56.0 (19/34)	[illegible] 28.0 (12/43)	20.0 (6/30)	0.0 (0/30)
Mortality	61.5 (8/13)	57.0 (31/57)	76.8 (53/69)	40.0 (20/50)	6.7 (9/54)

HSCT pts
78% S. prolificans
55% S. apiospermum

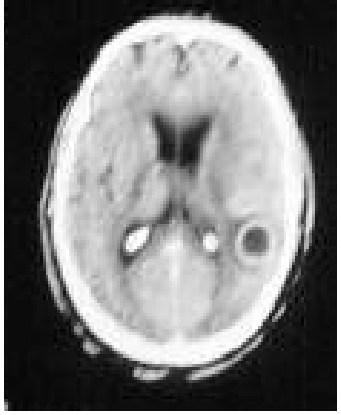
Scedosporiose

- Homme 42 ans
- 10 jours induction leucémie aigue myéloide
- Fièvre
- *Lomentospora prolificans*
- Voriconazole et terbinafine, transfusion de GB

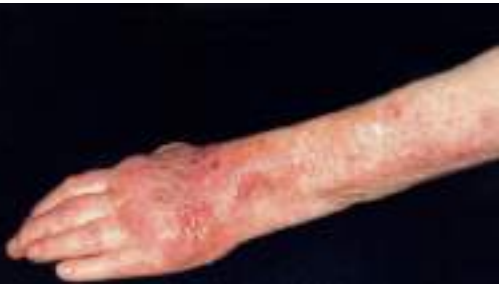




Differences between *S. apiospermum* complex and *Lomentospora prolificans*



	S. prolificans	*S. apiospermum*
Epidemiology	Rarer. Higher incidence in Spain and Australia	More frequent. Worldwide distribution
First case reported	1984: osteomyelitis	1898: Madura foot
Risk factors	Same incidence in immunocompetent and immunocompromised patients	Mainly in neutropenic patients
Clinical forms	Mycetoma; eye, osteoarticular, lung, CNS or skin infections	Mycetoma; osteomyelitis; eye, sinus, lung or CNS infections
Microbiological features	Brown–black hyphae commonly sporulate *in vivo*	Septate hyaline hyphae rarely sporulate *in vivo*
Diagnosis	Frequently positive blood cultures. Molecular methods, still investigational	Rarely positive blood cultures. Molecular methods, still investigational
Outcome (mortality rates)	85–100%	65–75%
In vitro susceptibilty	Broad-spectrum resistance	Voriconazole and posaconazole. Resistance to AmB and echinocandins



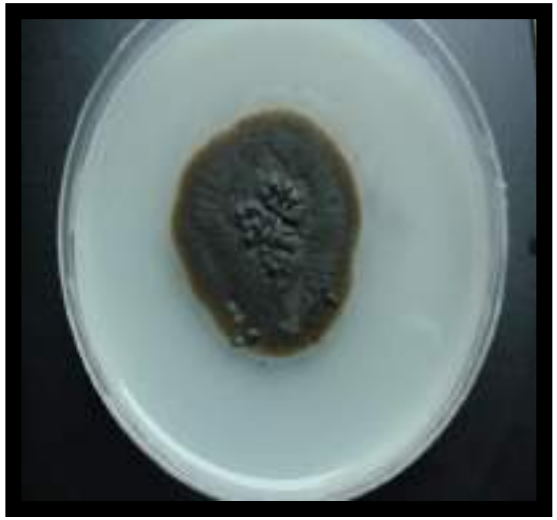
Caira, Exp Rev Antiinfect Ther 2011

Definitive diagnosis of scedosporiosis

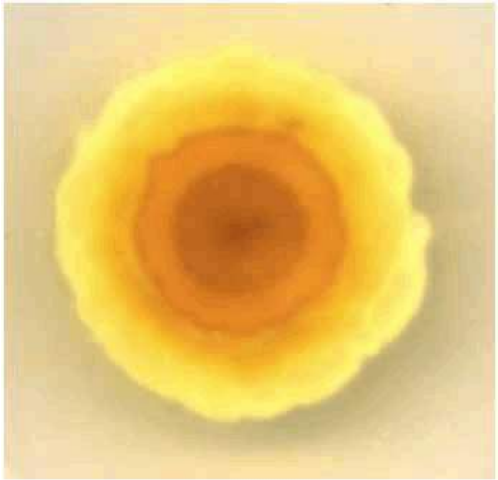
- Microscopic examination
- Culture : blood, fluids, tissue biopsy
- Molecular methods (ITS, calmodulin, Beta-tubulin)
- Histology: see infra

S. apiospermum

L. prolificans



S. aurantiacum (16% in Australia)



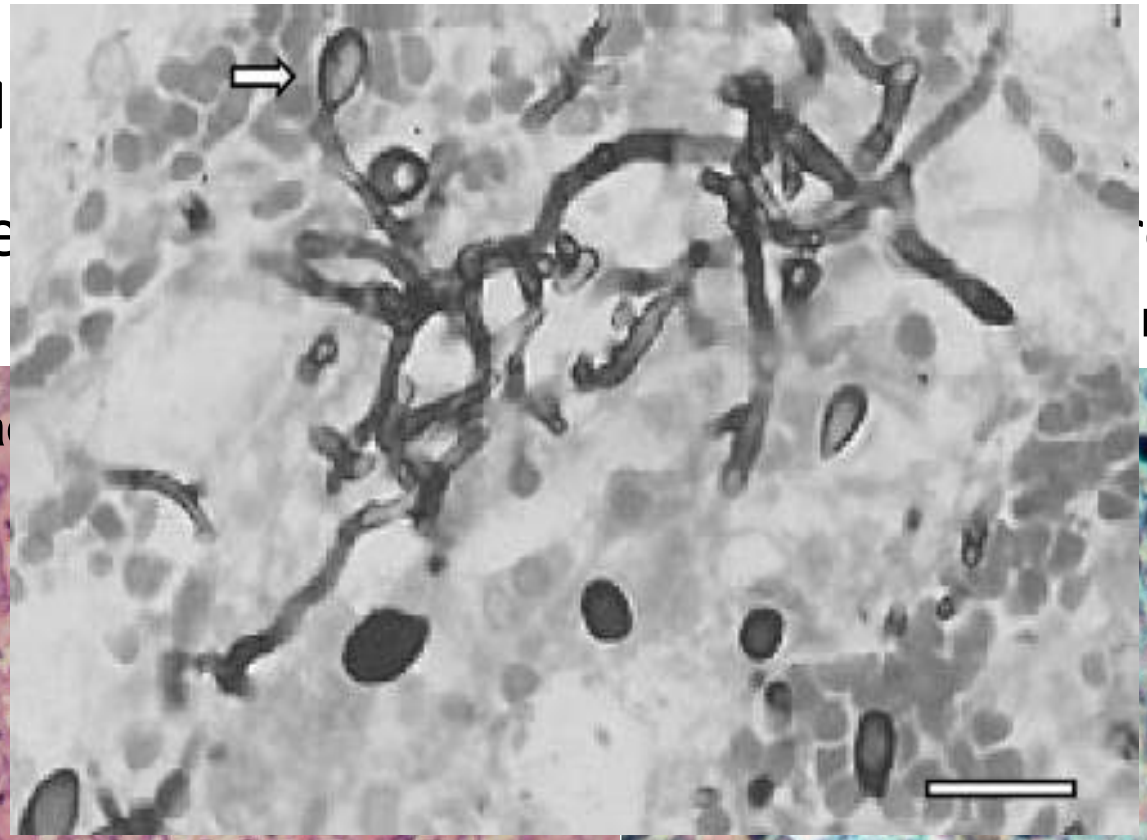
Heath, CMI 2009

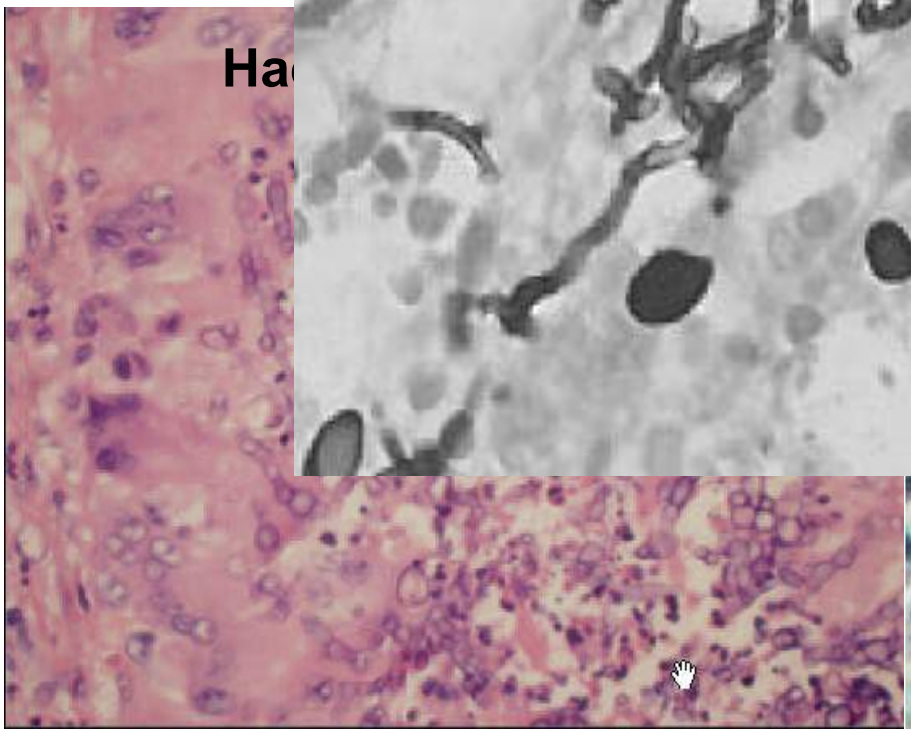
What is the role of histology?

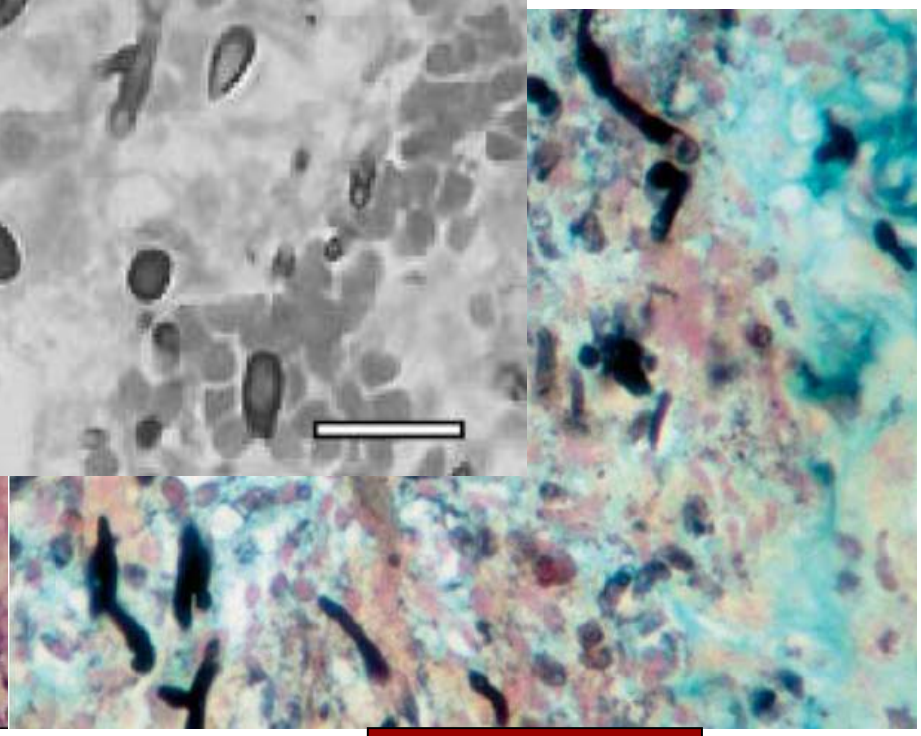
- M
- Re e present

mine silver stain

Ha







Ortoneda 2002

Courtesy: P Munoz

Scedosporium spp. : variable « resistance »

In vitro susceptibility of *Scedosporium* species

	AMB	ITRA	VORI	POSA	CASPO	TERBI	MICA
Scedosporium boydii (n=32)	8/≥8	0.5/2	0.25/0.5	0.5/1	1/2	≥8/≥8	0.25/1
Scedosporium apiospermum (n=62)	8/≥8	1/≥8	0.5/1	1/2	1/2	≥8/≥8	0.25/0.25
Scedosporium dehoogi (n=7)	≥8/-	0.5/-	0.5/-	0.5/-	2/-	≥8/-	0.25/-
Lomentospora prolificans (n=24)	8/≥8	≥8/≥8	8/≥8	≥8/≥8	4/8	≥8/≥8	4/≥8

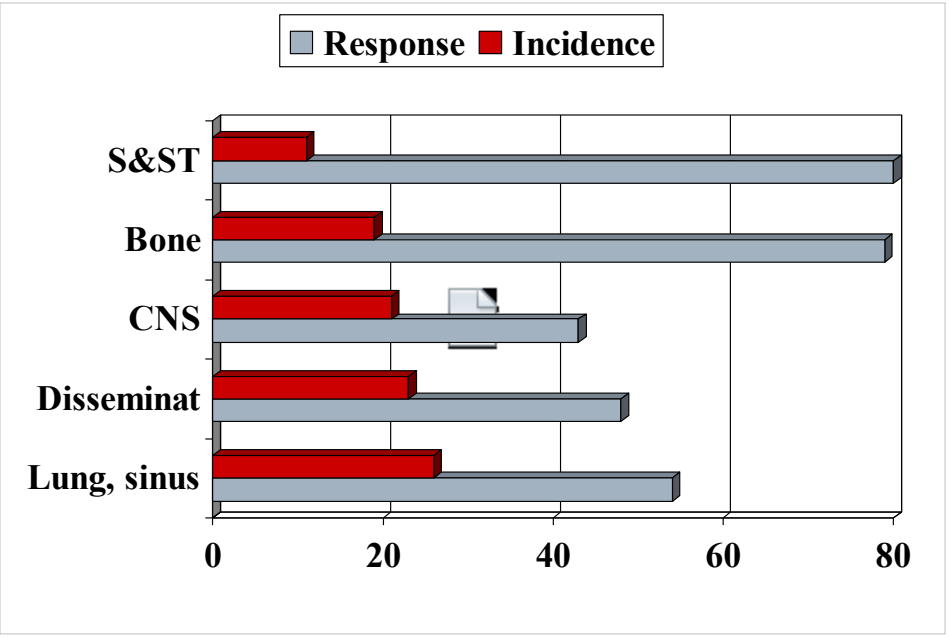
- NRCMA, unpublished data

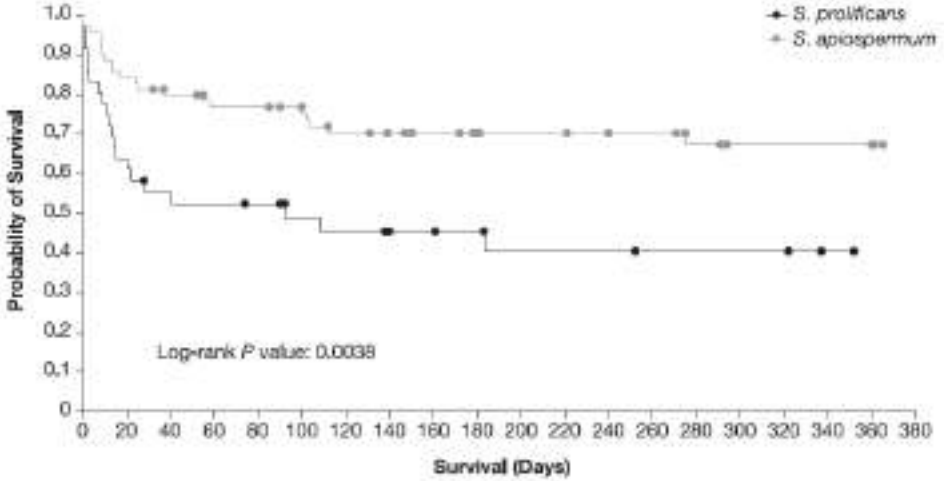
Treatment of Scedosporiosis with Voriconazole: Clinical Experience with 107 Patients[▽]

Peter Troke,[1]* Koldo Aguirrebengoa,[2] Carmen Arteaga,[3] David Ellis,[4] Christopher H. Heath,[5] Irja Lutsar,[6] Montserrat Rovira,[7] Quoc Nguyen,[8] Monica Slavin,[9] and Sharon C. A. Chen[10]
on behalf of the Global Scedosporium Study Group

- Voriconazole
  - Strong trend towards lower mortality (p = 0.06)

Total: 107
Response: 57%
S. apiospermum (70): 64%
S. prolificans (35): 44%
Median Therapy: 180d

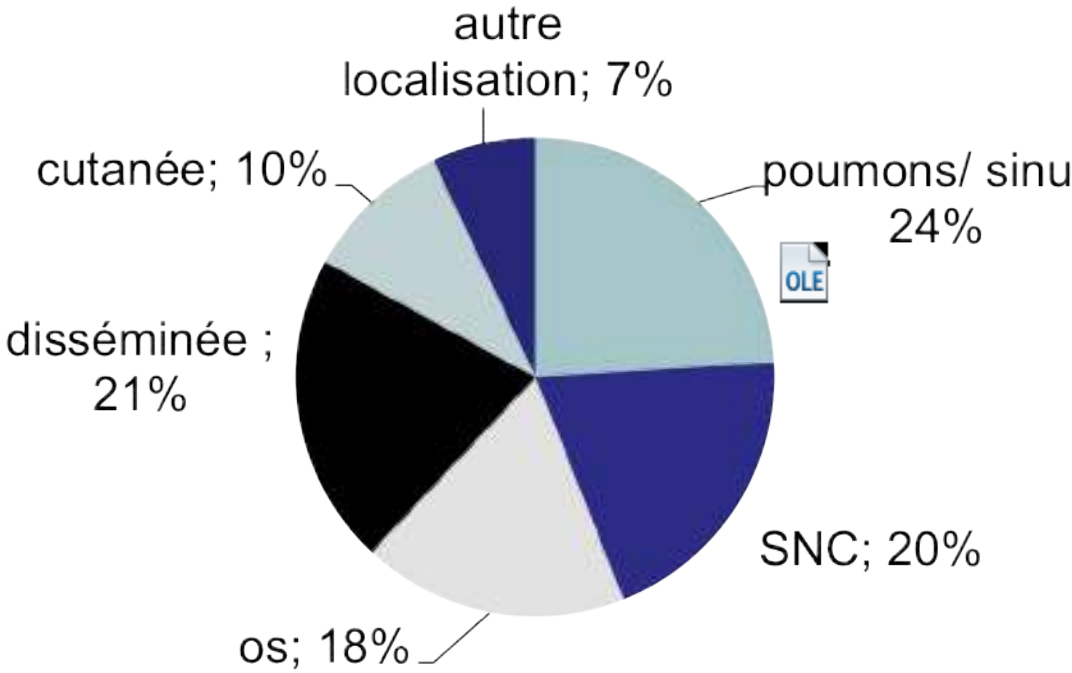




ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2008,

Scedosporium – traitement par voriconazole

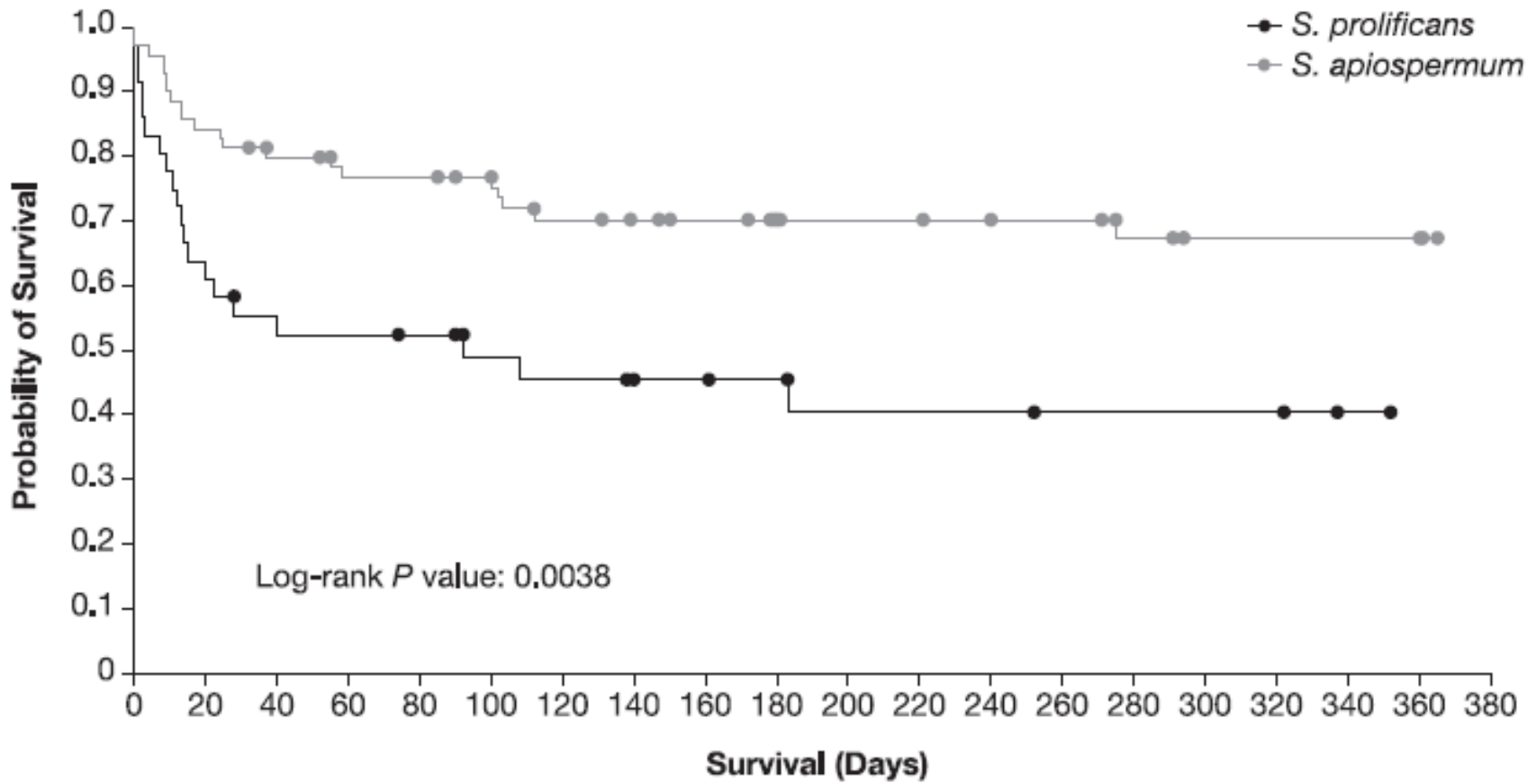
- Scedosporioses prouvées ou probables N=107
- 65% *S. apiospermum*
- SOT 22%, hémopathie maligne 21%, HSCT 9%



- 26% 1ère ligne
- Réponse au ttt : 57% (médiane de ttt 103 j)
- 47 décés, 73% attribuables

Troke et al, AAC 2008

Scedosporium - Pronostic



Troke, AAC 2008

IFSIG guidelines for first line treatment of scedosporiosis in immunodepressed patients

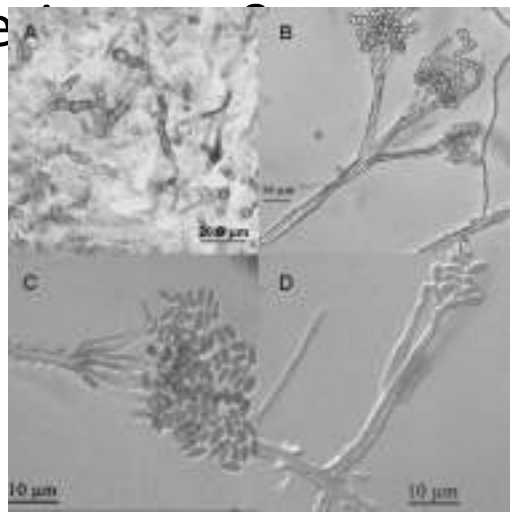
Treatment	SoR	QoR	Comment
Voriconazole	A	II	TDM
Itraconazole	D	III	
Combination	C	III	
L AmB	C	III	
Posaconazole	C	III	

CMI, 2014

Emergence of *Rasamsonia argillacea* in CGD patients

Emergence of Disseminated Infections Due to *Geosmithia argillacea* in Patients with Chronic Granulomatous Disease Receiving Long-Term Azole Antifungal Prophylaxis[7]

- Two cases of *G. argillacea* inf
- Prior ITZ ± VCZ
- Disseminated infections
- Multiply in vitro re
  clinical failure



Machouart, *JCM* 2011

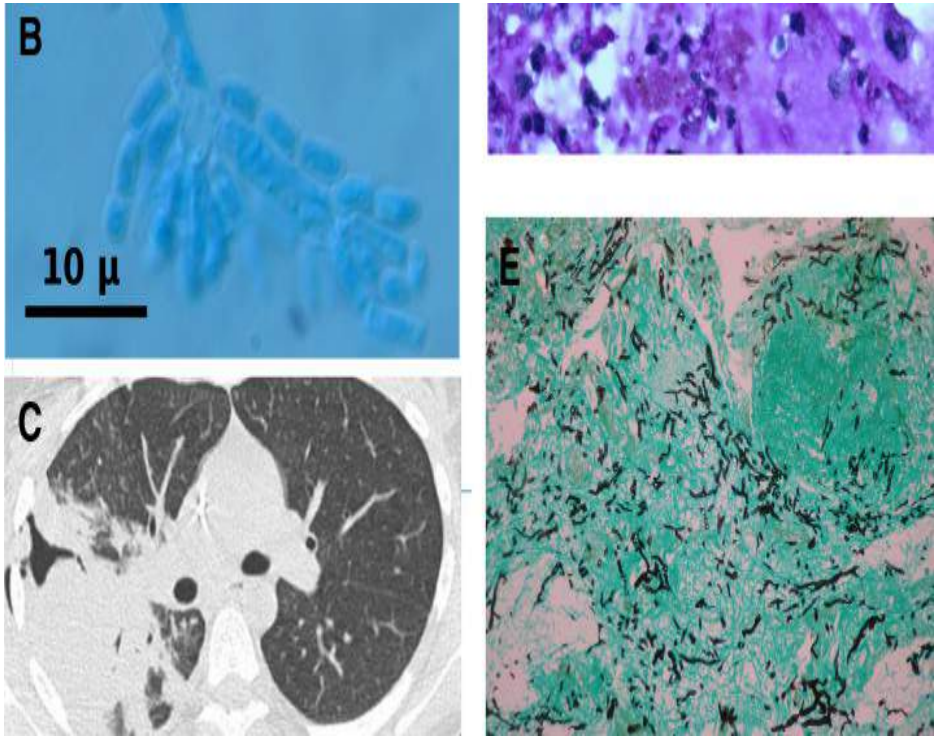
Geosmithia argillacea: An Emerging Cause of Invasive Mycosis in Human Chronic Granulomatous Disease

- 7 cases of *G. argillacea* inf
- 5 previously identified as *Paecilomyces variotii*
- Disseminated infections
- 3 deaths

De Ravin, *CID* 2011

New filamentous fungi in hematology

- *Hormographiella aspergillata*
- Basidiomycete
- Few reported cases
- Acute leukemia, allo HSCT
- Echinocandin resistant



Suarez F, *JCM* 2011

TRANSPLANT AND ONCOLOGY (MG ISON, SECTION EDITOR)

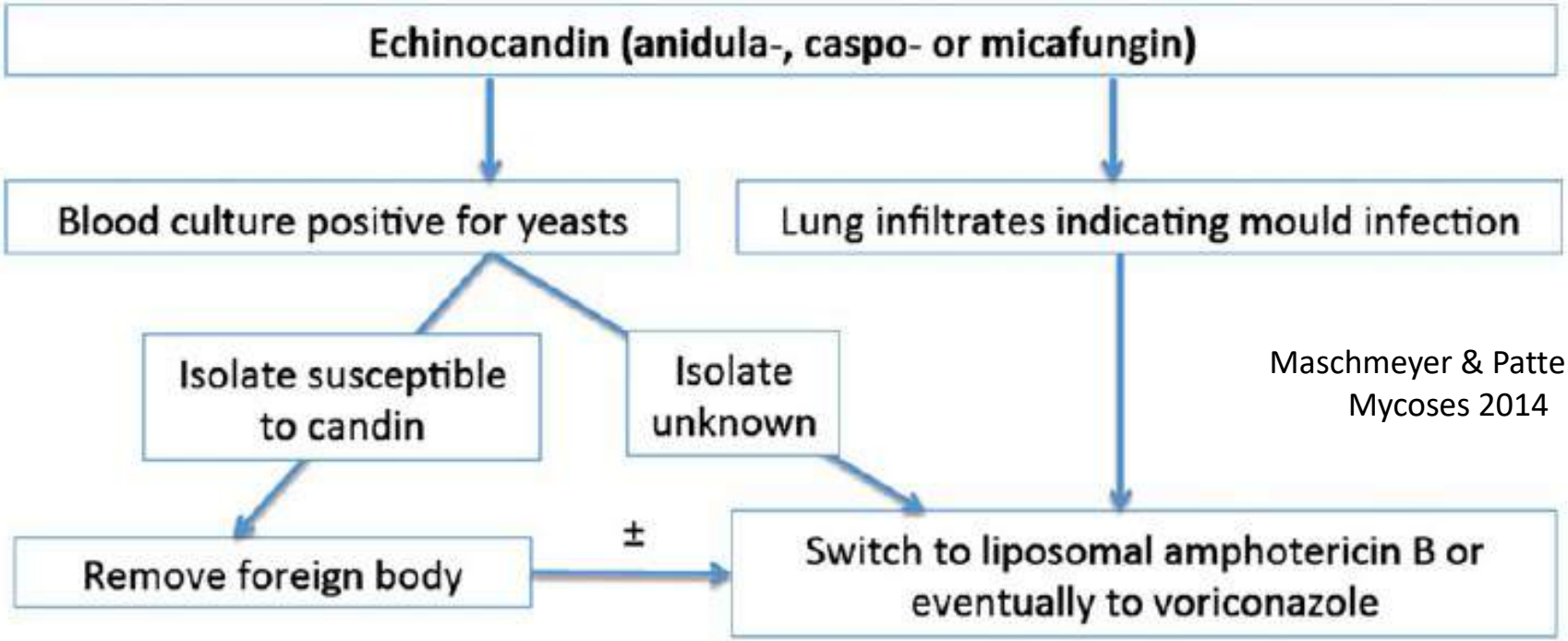
Curr Infect Dis Rep 2012

Emerging Invasive Fungal Diseases in Transplantation

Perrine Parize · Blandine Rammaert · Olivier Lortholary

- Many other rare molds from environment
- Previously considered as contaminants
  - *Acremonium* spp., *Phialemonium curvatum*
  - *Purpureocillium lilacinum/Paecilomyces variotii*
  - *Trichoderma* spp., *Scopulariopsis brevicaulis*
  - Phaeohyphomycetes, *Cokeromyces recurvatus,…*
- Outbreak: *Acremonium kiliense* catheter related fungemia
- ± detected by biomarkers (BDG / GM)!

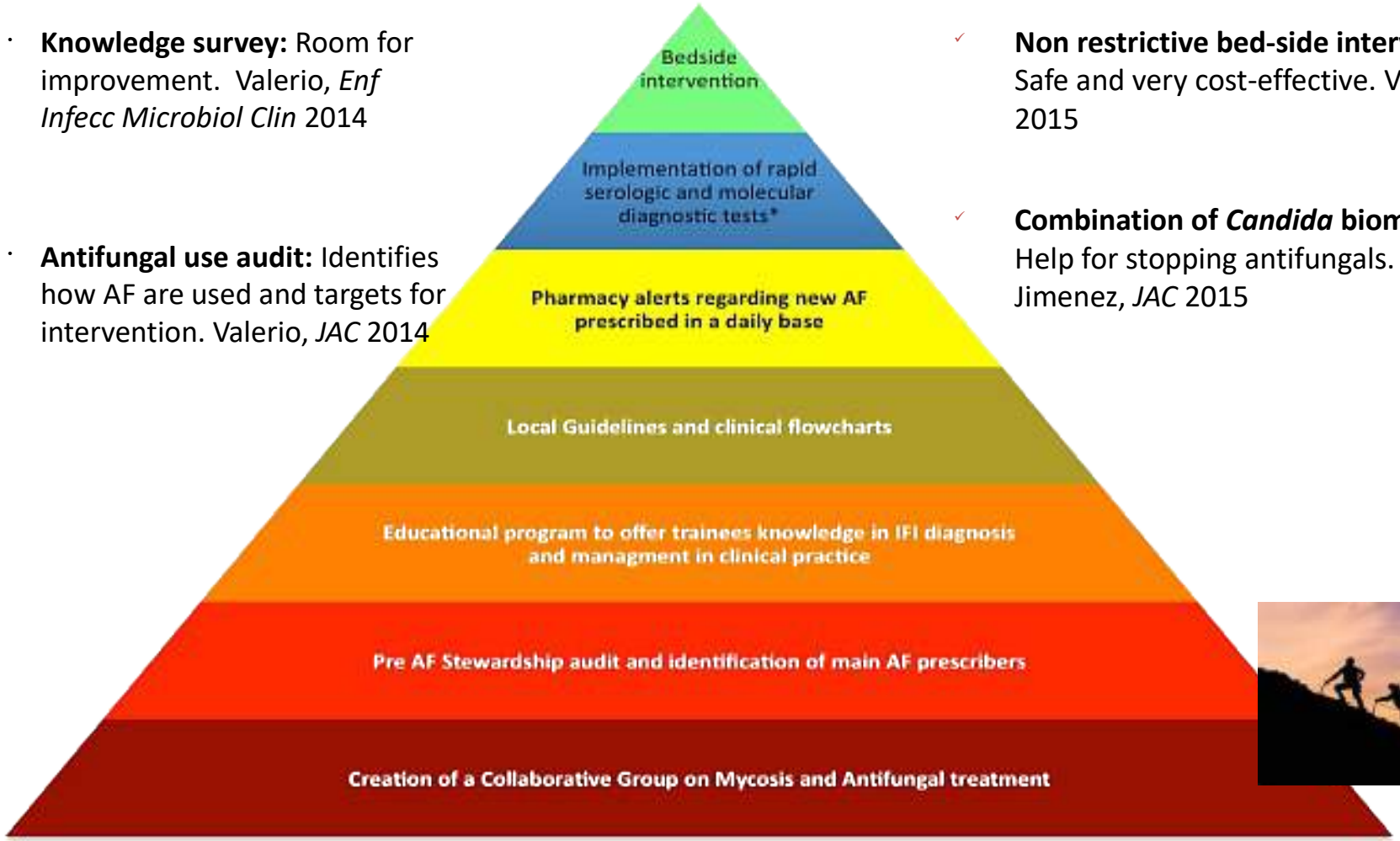
What to do in case of suspected mold infection during / shortly after echinocandin exposure?



Maschmeyer & Patterson
Mycoses 2014

Multidisciplinary antifungal stewardship programs: Madrid experience

- **Knowledge survey:** Room for improvement. Valerio, *Enf Infecc Microbiol Clin* 2014
- **Antifungal use audit:** Identifies how AF are used and targets for intervention. Valerio, *JAC* 2014

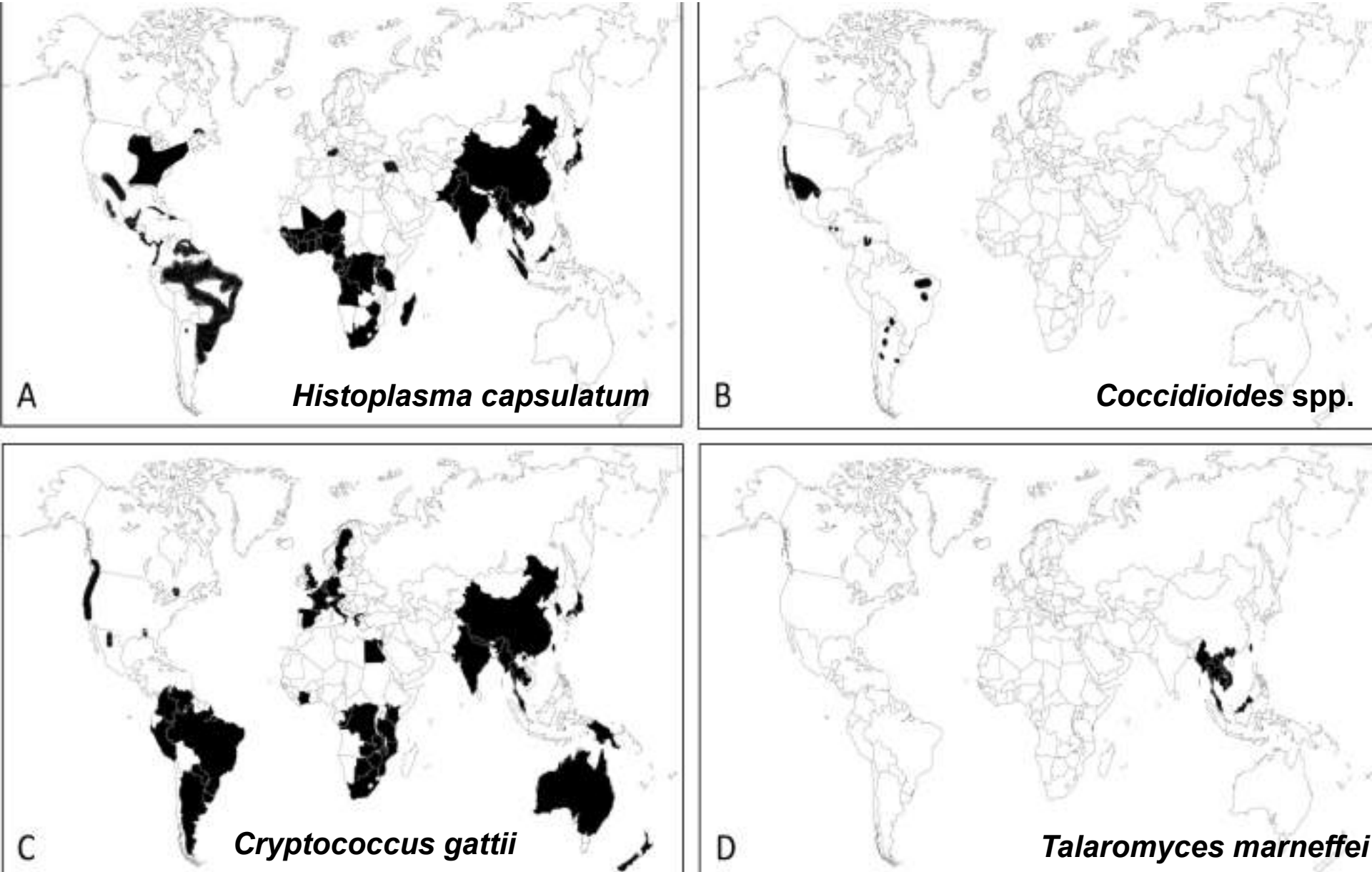


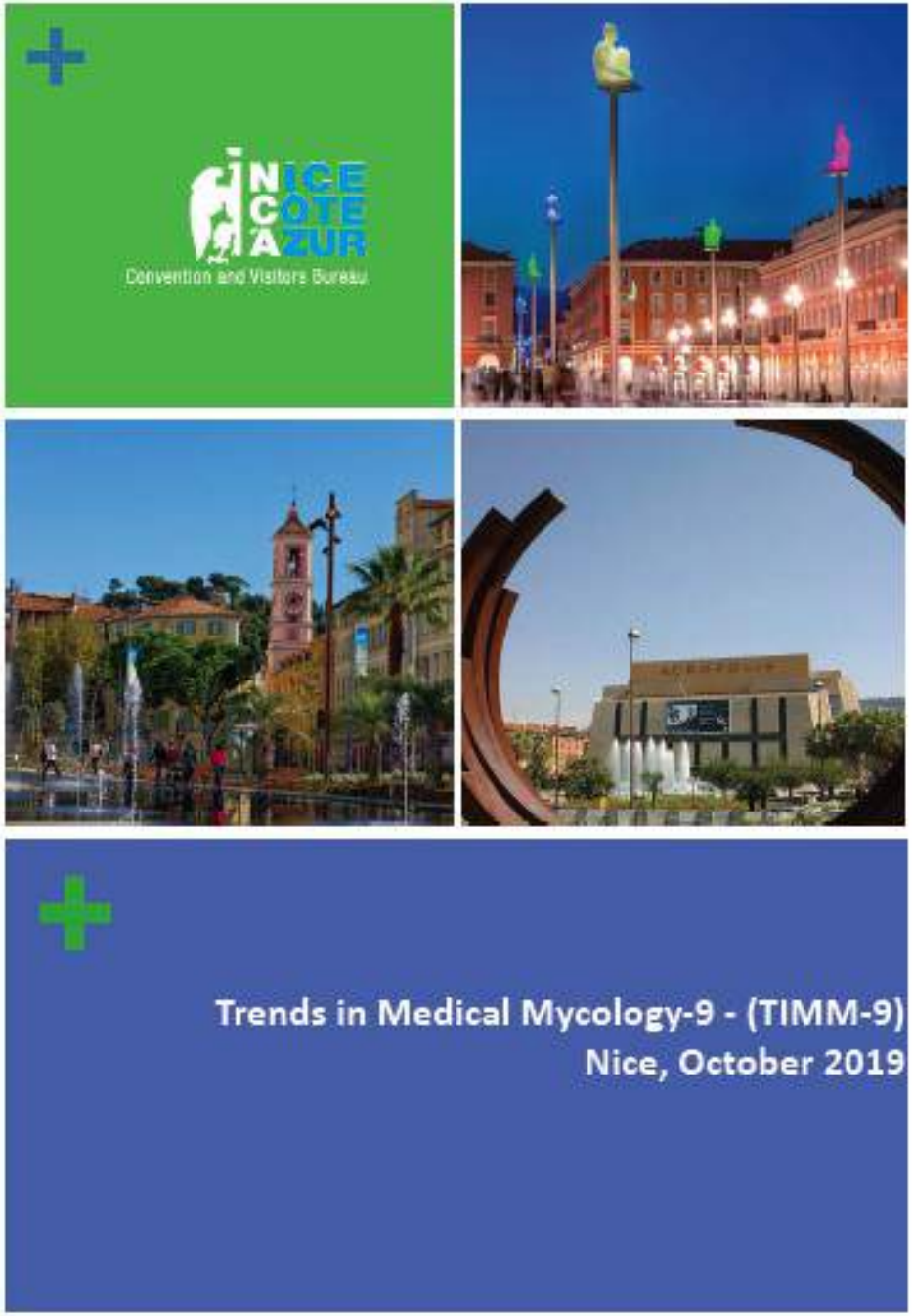
- ✓ **Non restrictive bed-side intervention:** Safe and very cost-effective. Valerio, *JAC* 2015
- ✓ **Combination of *Candida* biomarkers :** Help for stopping antifungals. Martinez-Jimenez, *JAC* 2015

Courtesy: P Munoz

Immunocompromised SOT and worldwide fungal risk

Lortholary O *et al*. CID 2013





See you in Nice!

Nice-Acropolis Convention Center