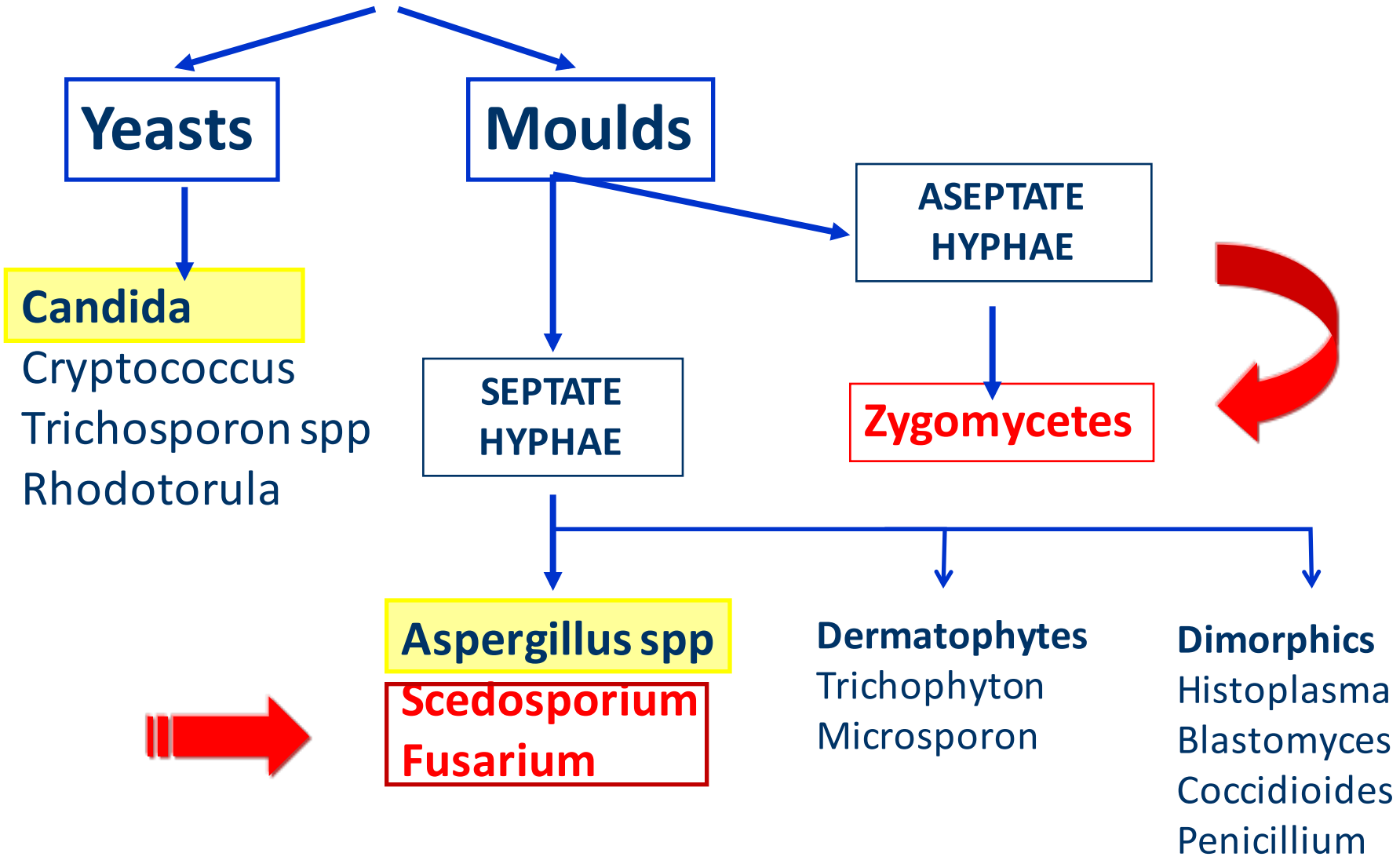
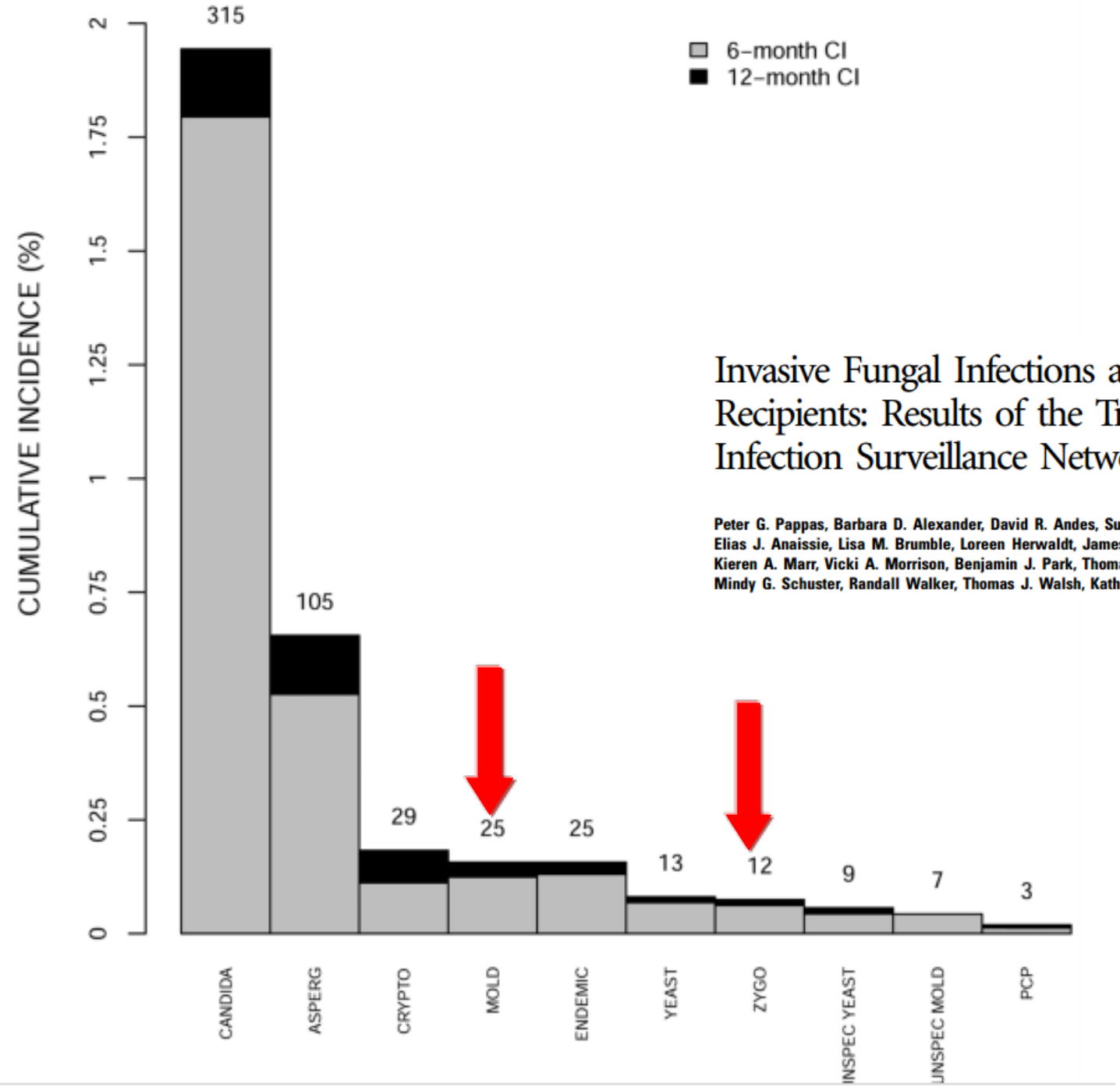
FUNGHI EMERGENTI (RARI)

Annamaria Nosari

Fungal agents



Modified from *de Pauw* et al, *Med J Hematol Infect Dis 2011*



Invasive Fungal Infections among Organ Transplant Recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

Peter G. Pappas, Barbara D. Alexander, David R. Andes, Susan Hadley, Carol A. Kauffman, Alison Freifeld, Elias J. Anaissie, Lisa M. Brumble, Loreen Herwaldt, James Ito, Dimitrios P. Kontoyiannis, G. Marshall Lyon, Kieren A. Marr, Vicki A. Morrison, Benjamin J. Park, Thomas F. Patterson, Trish M. Perl, Robert A. Oster, Mindy G. Schuster, Randall Walker, Thomas J. Walsh, Kathleen A. Wannemuehler, and Tom M. Chiller[a]

CID 2010

Invasive Non-*Aspergillus* Mold Infections in Transplant Recipients, United States, 2001–2006

Benjamin J. Park, Peter G. Pappas, Kathleen A. Wannemuehler, Barbara D. Alexander,

Table 1. Distribution of Mucorales, *Fusarium*, and *Scedosporium* organisms causing infection in HCT and SOT recipients, as detected in TRANSNET, United States, 2001–2006*

Organism	No. (%) patients		
	HCT	SOT	Total
Mucorales	77 (62.1)	28 (62.2)	105 (62.1)
Rhizopus spp.	39 (50.6)	16 (57.1)	55 (52.4)
Mucor spp.	12 (15.6)	7 (25.0)	19 (18.1)
Rhizomucor spp.	7 (9.1)	0	7 (6.7)
Cunninghamella spp.	5 (6.5)	4 (14.3)	9 (8.6)
Lichtheimia spp.†	3 (3.9)	0	3 (2.9)
Apophysomyces spp.	1 (1.3)	0	1 (1.0)
Syncephalastrum spp.	1 (1.3)	0	1 (1.0)
Unspecified	9 (11.7)	1 (3.6)	10 (9.5)
Genus *Fusarium*	31 (25.0)	6 (13.3)	37 (21.9)
F. solani	9 (29.0)	1 (16.7)	10 (27.0)
F. oxysporum	0	2 (33.3)	2 (5.4)
F. proliferatum	2 (6.5)	0	2 (5.4)
F. verticilloides	1 (3.2)	0	1 (2.7)
Unspecified	19 (61.3)	3 (50.0)	22 (59.5)
Genus *Scedosporium*	16 (12.9)	11 (24.4)	27 (16.0)
S. apiospermum	13 (81.3)	6 (54.5)	19 (70.4)
S. prolificans	3 (18.8)	5 (45.5)	8 (29.6)
Total	124 (73.4)	45 (26.6)	169 (100)

1208 SOT recipients
166 cases of non-Aspergillus molds
The Mucorales (105 patients) were the most common of these molds, followed by Fusarium spp. (37 pts), and Scedosporium spp. (27 pts).

Emerg Infect Dis 2011

Invasive Non-*Aspergillus* Mold Infections in Transplant Recipients, United States, 2001–2006

Benjamin J. Park, Peter G. Pappas, Kathleen A. Wannemuehler, Barbara D. Alexander,

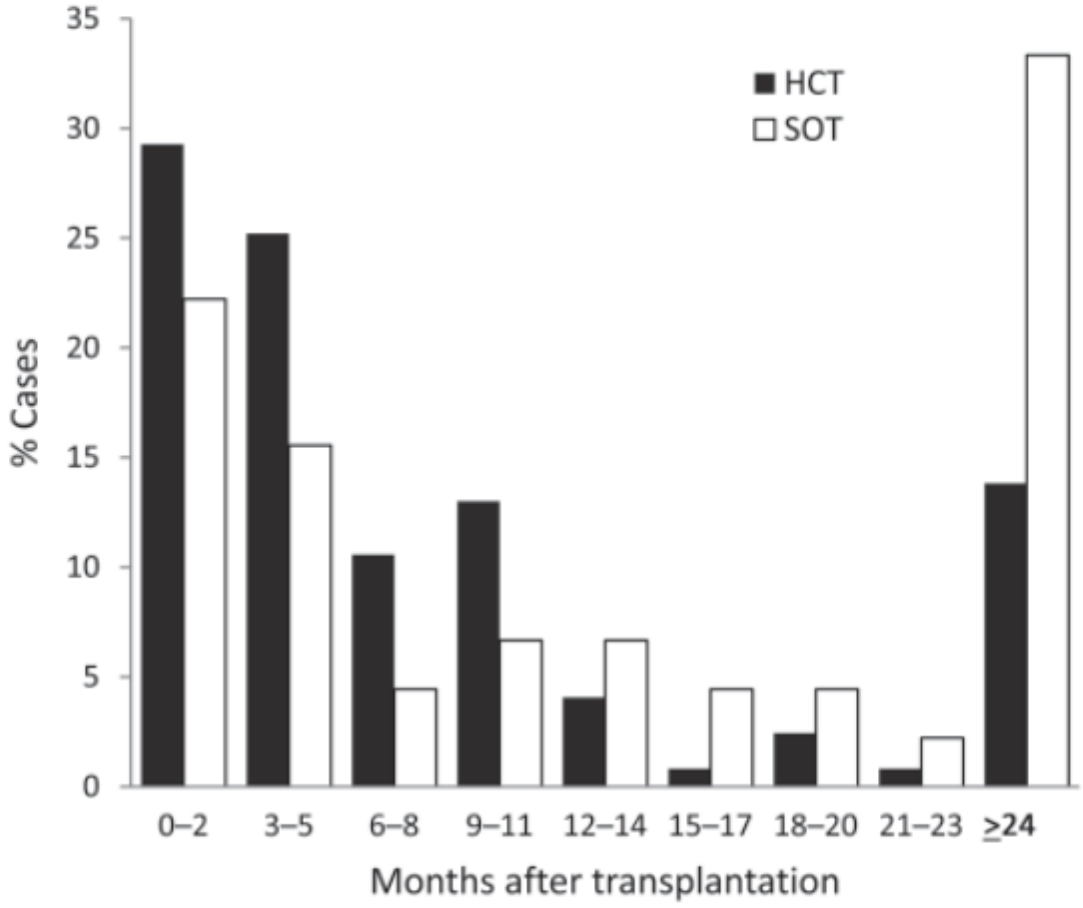


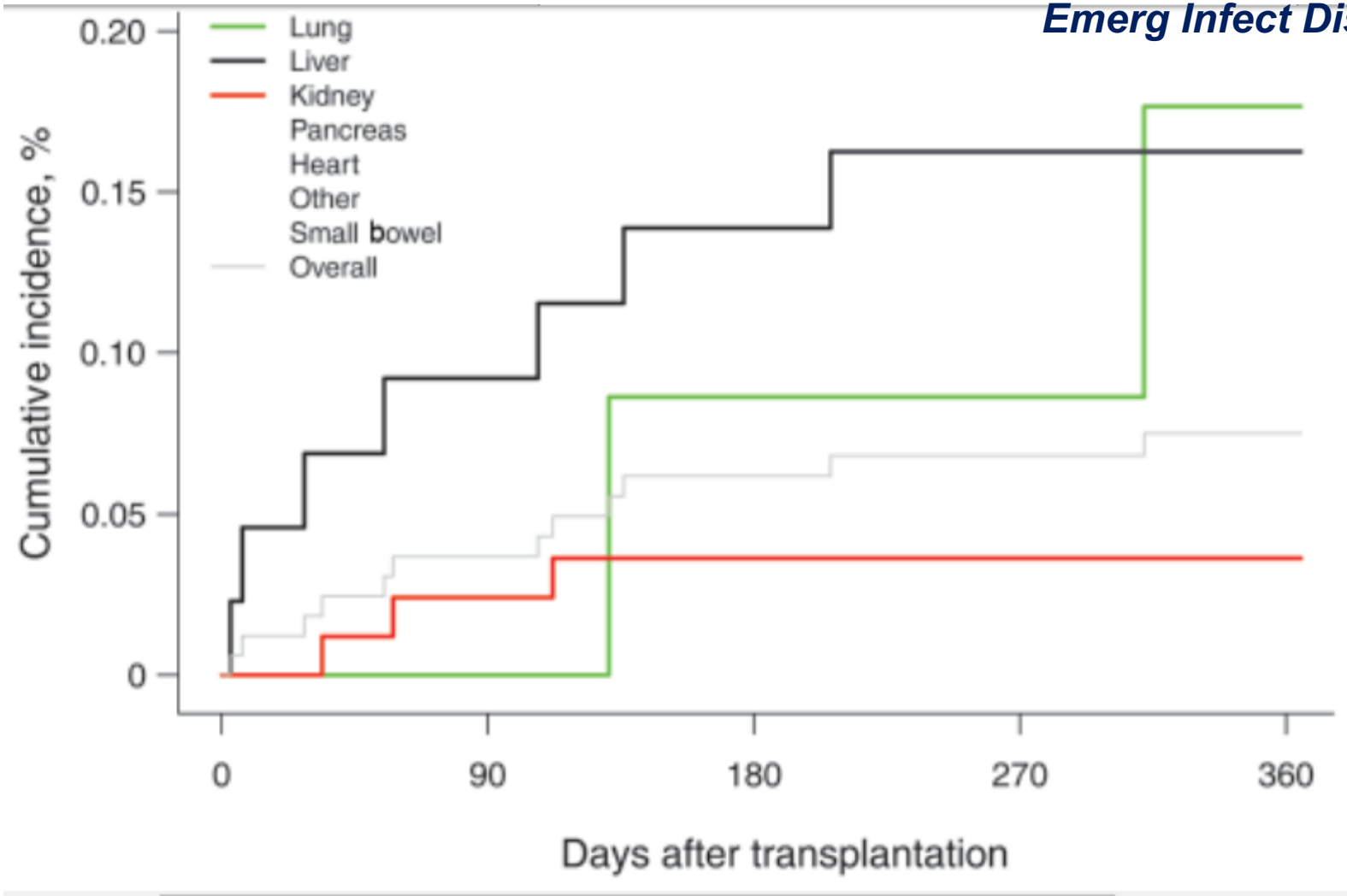
Figure 1. Months from transplant to development of invasive mucormycosis, fusariosis, or scedosporiosis among hematopoietic

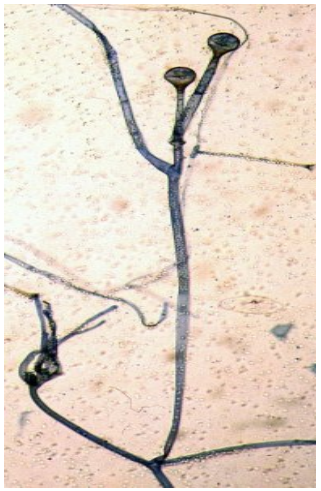
Emerg Infect Dis 2011

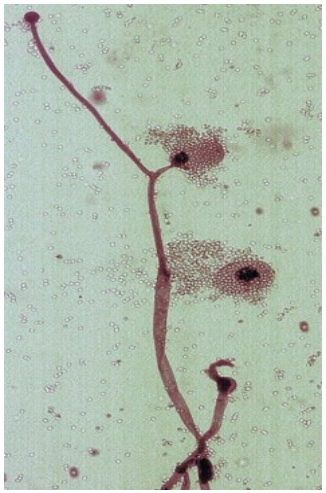
Invasive Non-*Aspergillus* Mold Infections in Transplant Recipients, United States, 2001–2006

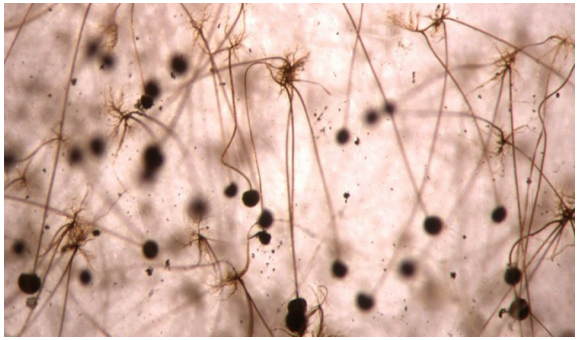
Benjamin J. Park, Peter G. Pappas, Kathleen A. Wannemuehler, Barbara D. Alexander,

Emerg Infect Dis 2011







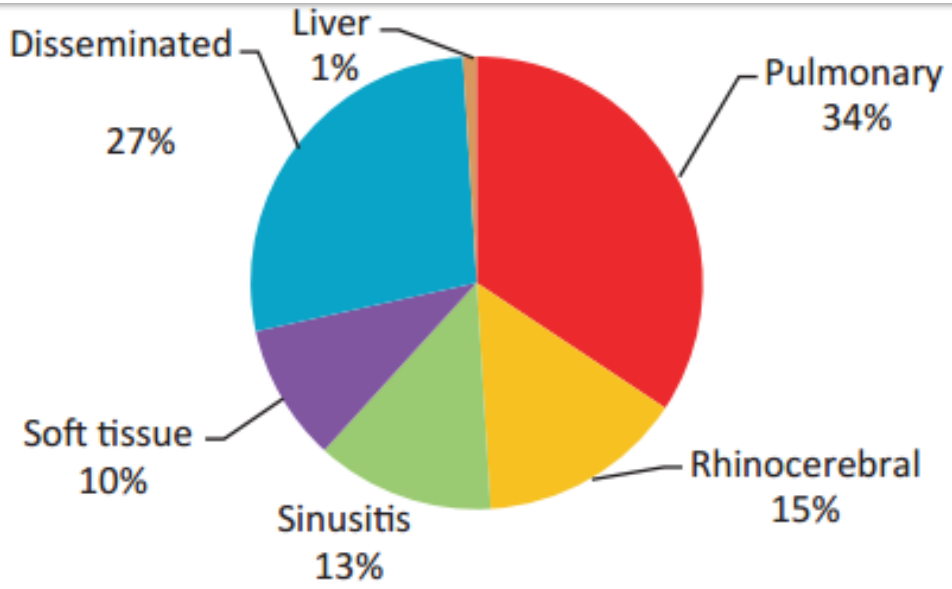


Mucorales are characterized by wide hyphae (10-20 mm), irregularly shaped, with acute angle ramifications.

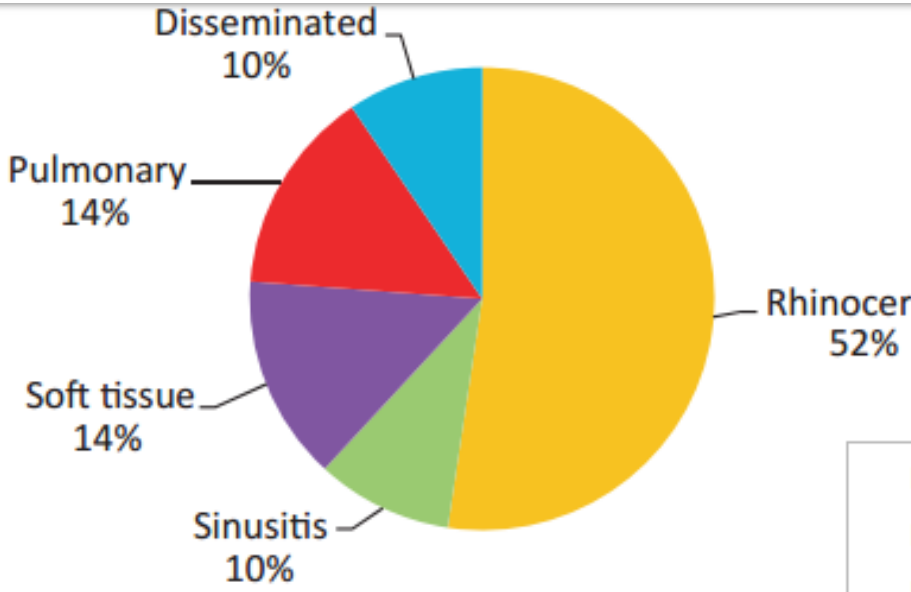
They are ubiquitarian, saprophytic, aerobic agents, that find an otpimal substratum for their growth in meat and sugar at a temperature of about 25° C-35° C

Classes of “high risk” patients for Mucormycosis

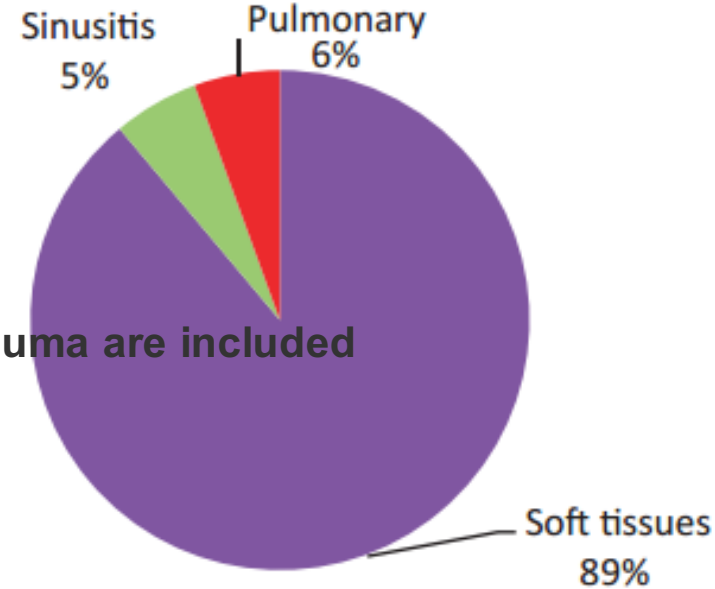
- Substratum with high acidity (Ketoacidosis)
- Macrophage inhibition in controlling spores germination (steroids = Autoimmune diseases)
- Altered neutrophils chemotaxis (Diabetes)
- Ferrioxamine transformation in ferrirhizoferrin (IRC and Trasfusion overload recipients)
- Immunosuppressive therapy (graft = HSCT and SOT)
- NEUTROPENIA (hematological malignancy= ↑↑AML)



Haematological malignancies ($n = 102$)



Diabetes ($n = 21$)

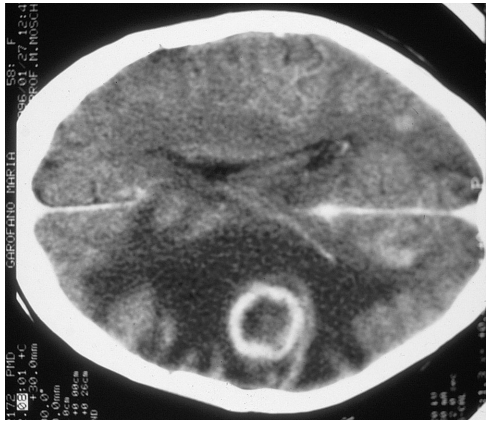


No underlying disease (n = 18)
Immunocompetent patients with trauma are included

Skiada CMI 2011

The most frequent infection form is the **rino-cerebral** one, linked to the capability of fungi to penetrate in the body through nasal and nosepharyngeal mucosa (typical of diabetic patient)

In neutropenic patients can be instead more easily observed the picture of **mycotic pneumonia** with a penetration mechanism similar to the previous one



Gemelli

Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007

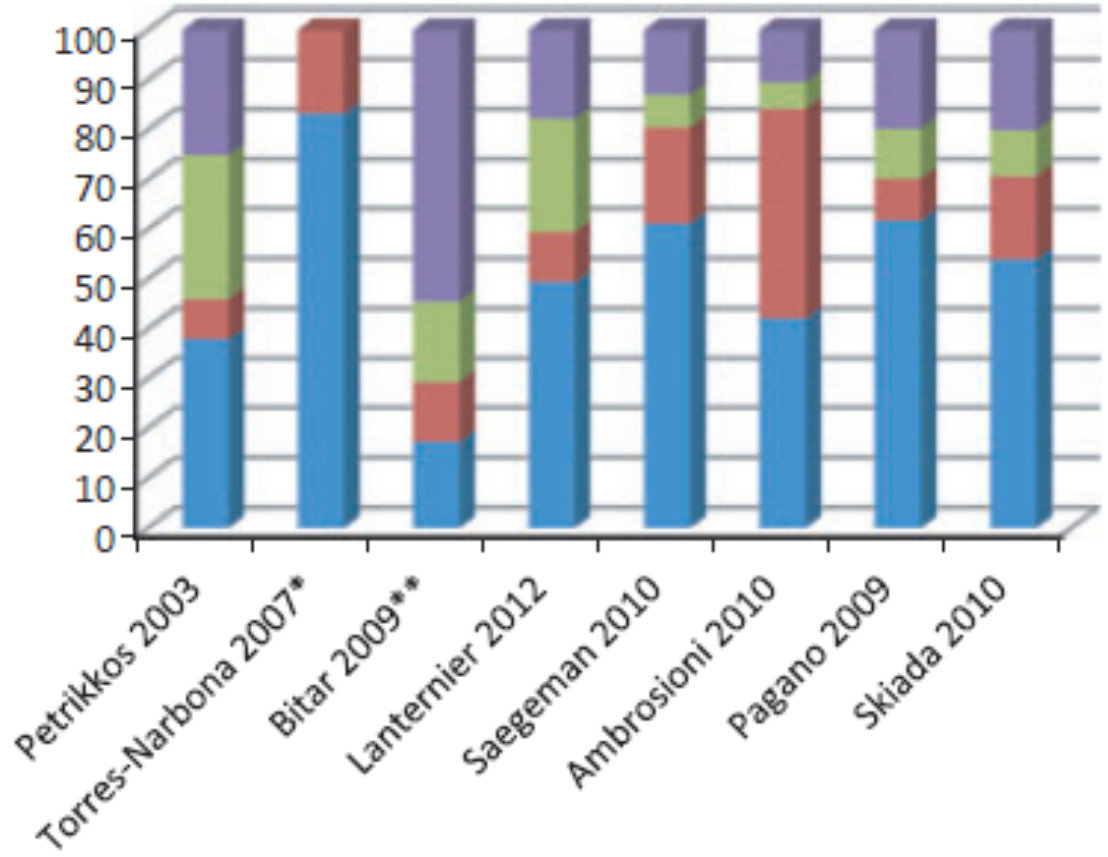
A. Skiada[1], L. Pagano[2], A. Groll[3], S. Zimmerli[4], B. Dupont[5], K. Lagrou[6], C. Lass-Florl[7], E. Bouza[8], N. Klimko[9], P. Gaustad[10], M. Richardson[11], P. Hamal[12], M. Akova[13], J. F. Meis[14], J.-L. Rodriguez-Tudela[15], E. Roilides[16], A. Mitrousia-Ziouva[17] and G. Petrikkos[18] for the European Confederation of Medical Mycology Working Group on Zygomycosis*

sis and mortality[a]

Underlying condition	Number of patients (%)	Number of patients who died (%)[b]
Haematological malignancies[c]	102 (44)	49/95 (52)
Acute myeloid leukaemia	49/102 (48)	
Acute lymphoblastic leukaemia	22/102 (22)	
Non-Hodgkin lymphoma	11/102 (11)	
Myelodysplastic syndrome	6/102 (6)	
Other	12/102 (12)	
Haematopoietic stem cell transplantation[d]	21 (9)	13/17 (76)
Other malignancies	11 (5)	5/9 (56)
Solid organ transplantation	10 (4)	5/10 (50)
Diabetes mellitus	39 (17)	18/33 (55)
Trauma	39 (17)	13/32 (41)
Burn	7 (3)	2/6 (33)
HIV/AIDS	4 (2)	0/3 (0)
Aplastic anaemia	4 (2)	1/4 (25)
Other[e]	9 (4)	4/9 (44)

CMI 2011

Epidemiology of mucormycosis in Europe



Case-series collected between 1993-2007

GR	SPA	FRA	FRA	BEL	CH	ITA	EU
Mono	Multi	Multi	Multi	Mono	Mono	Multi	Multi
24	6	531	101	31	19	60	230

Petrikkos et al. CMI 2014

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 9, September 2010

Increasing Incidence of Mucormycosis in University Hospital, Belgium

Veroniek Saegeman, Johan Ma
Wouter Meersseman, Isabel S
Eric Verbeken, and Katrien La

Over a 10-year period
31 proven/probable cases

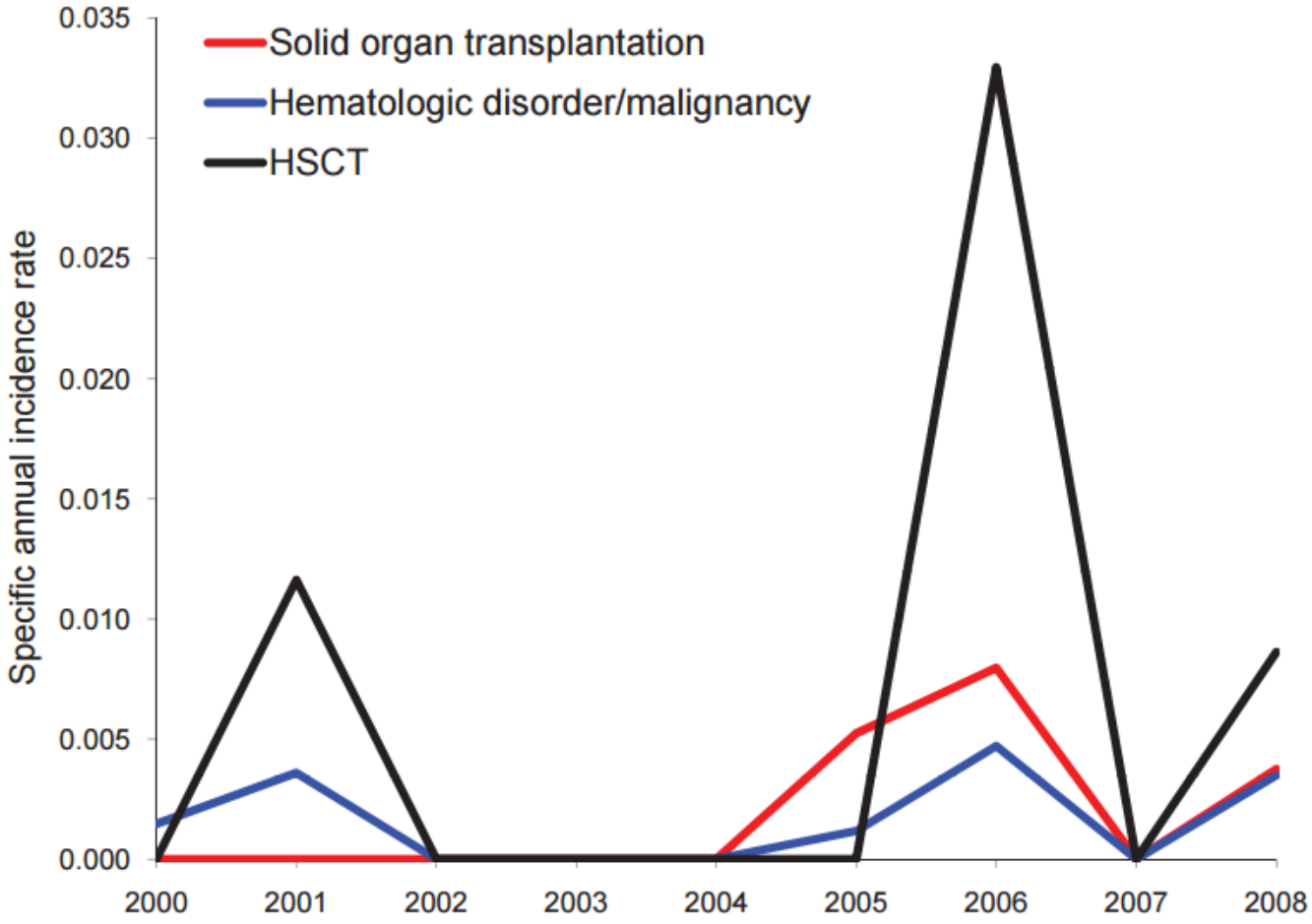


Figure 2. Specific annual incidence rate for the risk groups solid

Zygomycosis in Solid Organ Transplant Recipients: A Prospective, Matched Case-Control Study to Assess Risks for Disease and Outcome

J Infect Dis 2009

Nina Singh, Jose M. Aguado, Hugo Bonatti, Graeme Forrest, Krishan L. Gupta, Nasia Safdar, George T. John,

50 pts with zygomicosis and 50 controls from 2003 through 2007

- **the success rate among case patients was 60%** (30 of 50 patients).
- In 4 case patients the diagnosis of zygomycosis was made at autopsy
- 5 received 7 days of antifungal therapy before death (9 dead pts)
- the initial treatment consisted of L-AmB in 17 (42%), AmB lipid complex in 8 (20%), AmB deoxycholate in 5 (12%), posaconazole in 5 (12%), and a combination of antifungal agents in 6 (15%)

Zygomycosis in Solid Organ Transplant Recipients: A Prospective, Matched Case-Control Study to Assess Risks for Disease and Outcome

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J Infect Dis 2009

Table 3. Risk Factors for Zygomycosis in the 50 Case Patients with Zygomycosis, Compared with Paired Control Patients

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.02 (0.99–1.04)	.213	…	
Retransplant	6.9 (1.6–31.0)	.011	5.67 (0.86–37.5)	.072
Diabetes mellitus	3.8 (1.51–9.39)	.004	8.11 (2.70–24.4)	<.001
Prior rejection	2.9 (1.1–7.5)	.03	2.62 (0.79–8.71)	.115
Renal failure at baseline	2.7 (1.3–5.4)	.006	3.17 (1.31–7.65)	.010
Dialysis at baseline	3.2 (1.4–7.5)	.007	…	
Cytomegalovirus infection	1.7 (0.42–6.88)	.451	…	
Prior voriconazole or caspofungin use	10.9 (1.4–85.2)	.002	4.41 (1.12–17.3)	.033
Immunosuppression				
Tacrolimus	0.52 (0.30–0.88)	.016	0.23 (0.09–0.57)[a]	.002
Cyclosporine A	1.5 (0.79–2.9)	.206	…	
Sirolimus	4.3 (0.43–42.0)	.215	…	
T cell antibodies				
Any	1.0 (0.5–1.9)	.99	…	
Depleting	1.2 (0.5–2.6)	.66	…	
Nondepleting	1.0 (0.5–2.1)	.99	…	

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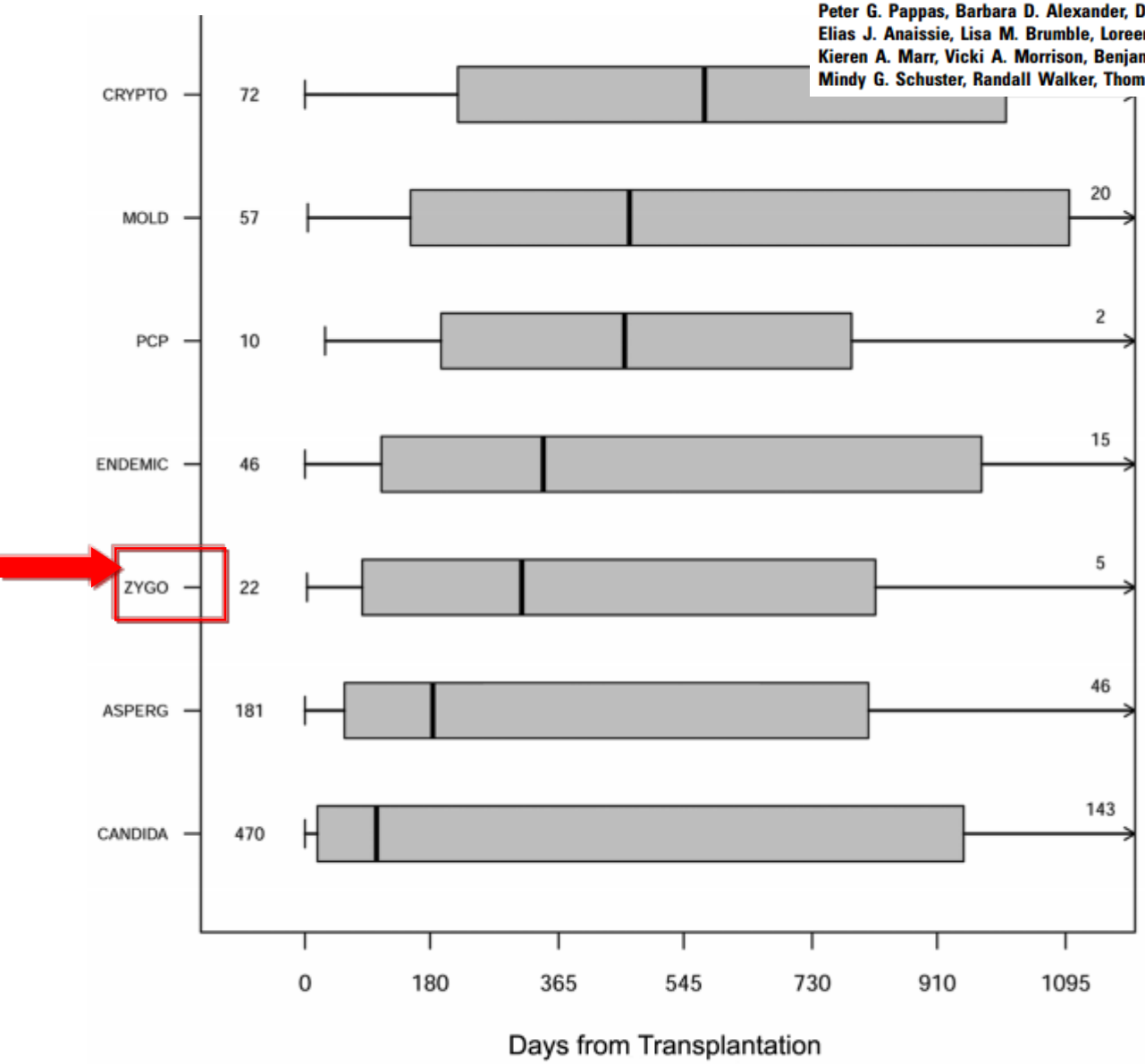
CID 2010



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]

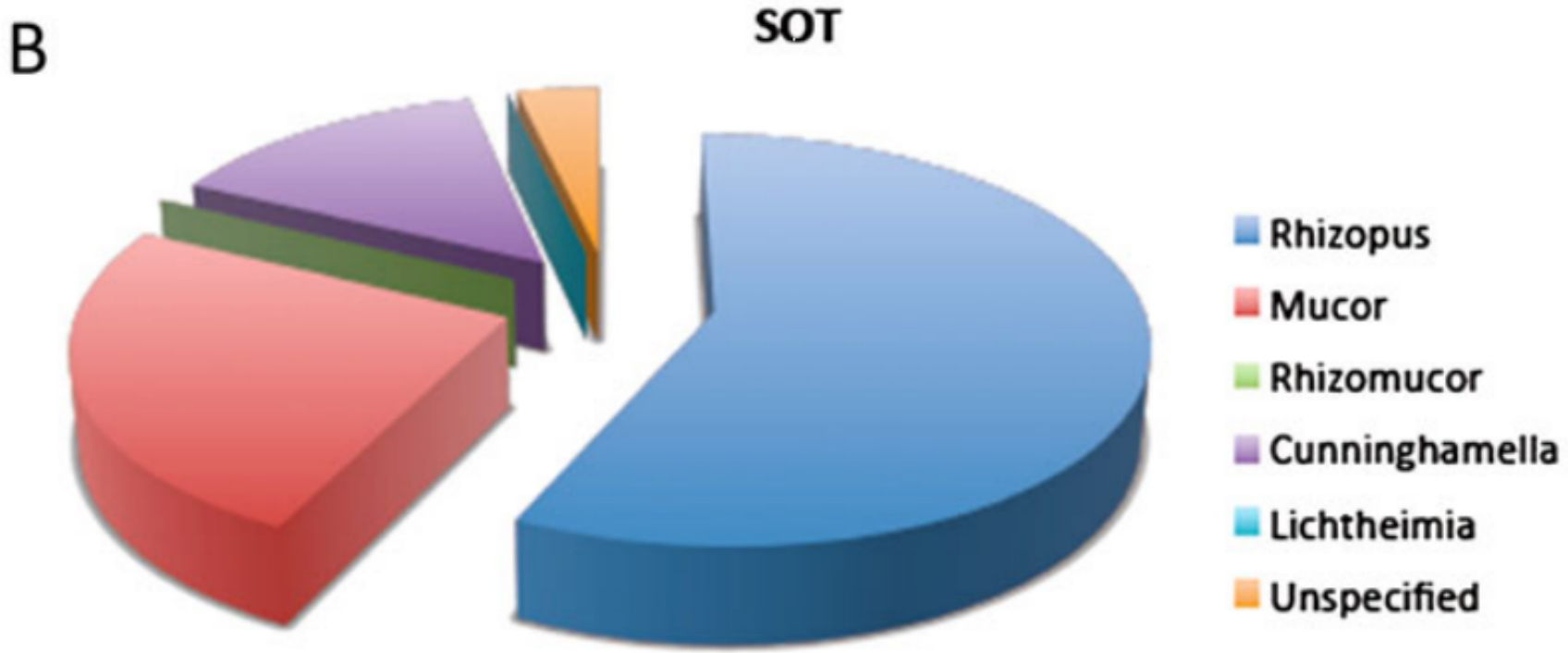
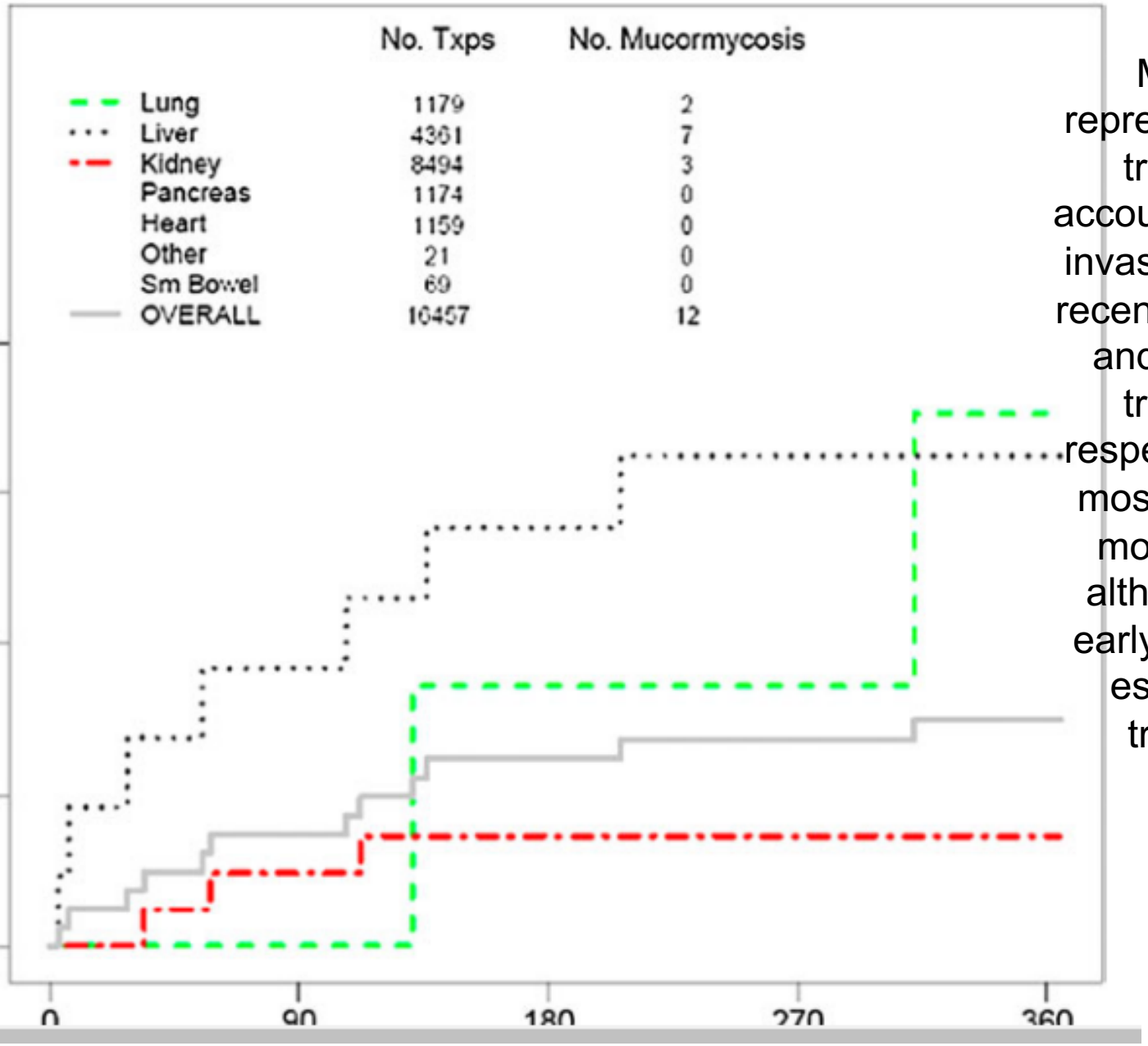


Figure 4. Distribution of Mucorales species among hematopoietic stem-cell transplant (HSCT; *A*) and solid-organ transplant (SOT; *B*) recipients in the TRANSNET study (adapted from Park et al, *Emerg Infect Dis* 2011 [18], with permission from B. Park).

Lanternier CID 2012

Lanternier CID 2012



Mucormycosis now represents a major threat in transplant recipients, accounting for 2% and 8% of invasive fungal infections in recent cohorts of solid-organ and allogeneic stem-cell transplant recipients, respectively. Mucormycosis most often occurs late, >3 months after transplant, although cases occurring early have been observed, especially among liver transplant recipients

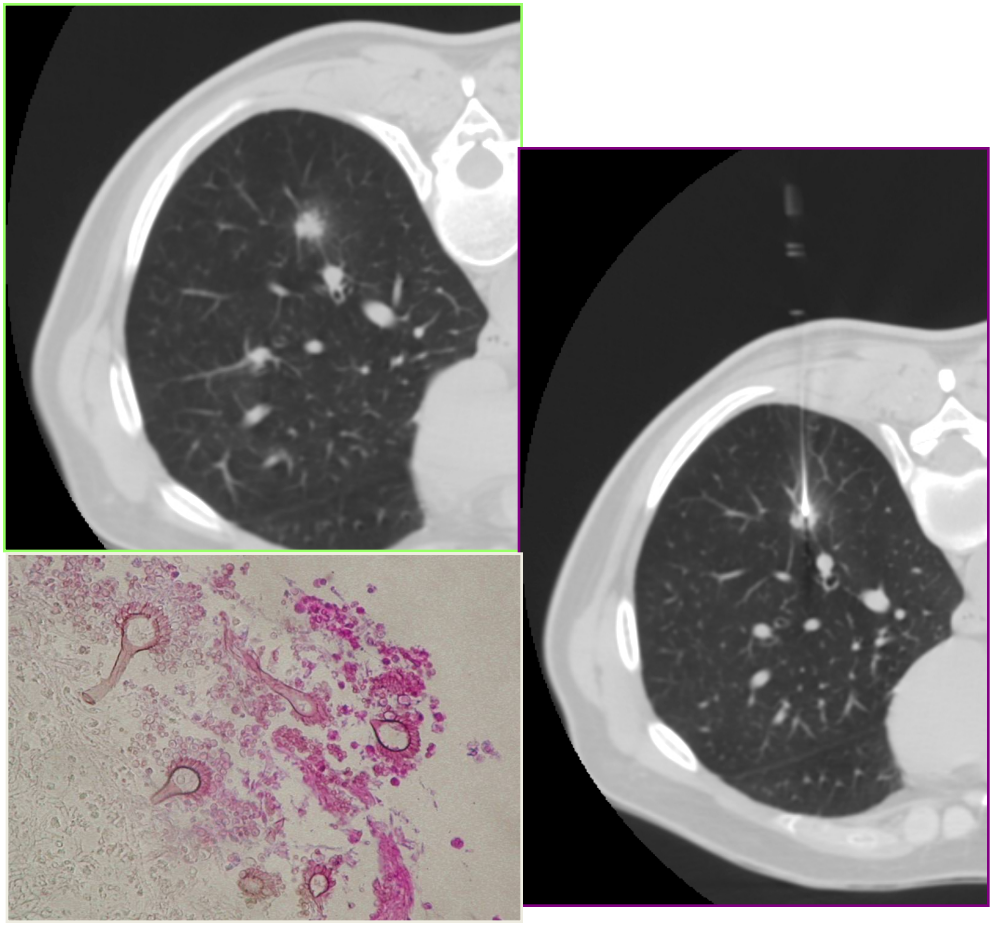
The overall mortality rate among SOT with mucormycosis is 38%–48%

Int J Hematol. 2009 Jun; 89(5):624-7. Epub 2009 May 27.

Role of CT-guided percutaneous lung biopsy in diagnosis of pulmonary fungal infection in patients with hematologic diseases.

Shi JM, Cai Z, Huang H, Ye XJ, He JS, Xie WZ, Zhang J, Zhou XY, Luo Y, Lin Y, Li L, Zheng WY, Wei GQ, Lin MF.

- Optimal for PCR-based diagnosis
- Complications <1%.
- NO false positivity (NO CONTAMINATION)
- Sensibility 80%; PPV 100%
- Diagnosis in 53% of not diagnostic BAL



Laas-Florl et al Clin Infect Dis 2007
Gupta S. Hematologic Oncology 2009

Nosari A et al, Haematologica 2003
Carrafiello G et al Radiol Med 2006

Diagnosi

Galactomannan

mold active prophylaxis decrease the predictive value (low incidence of IA)

serum GM assay

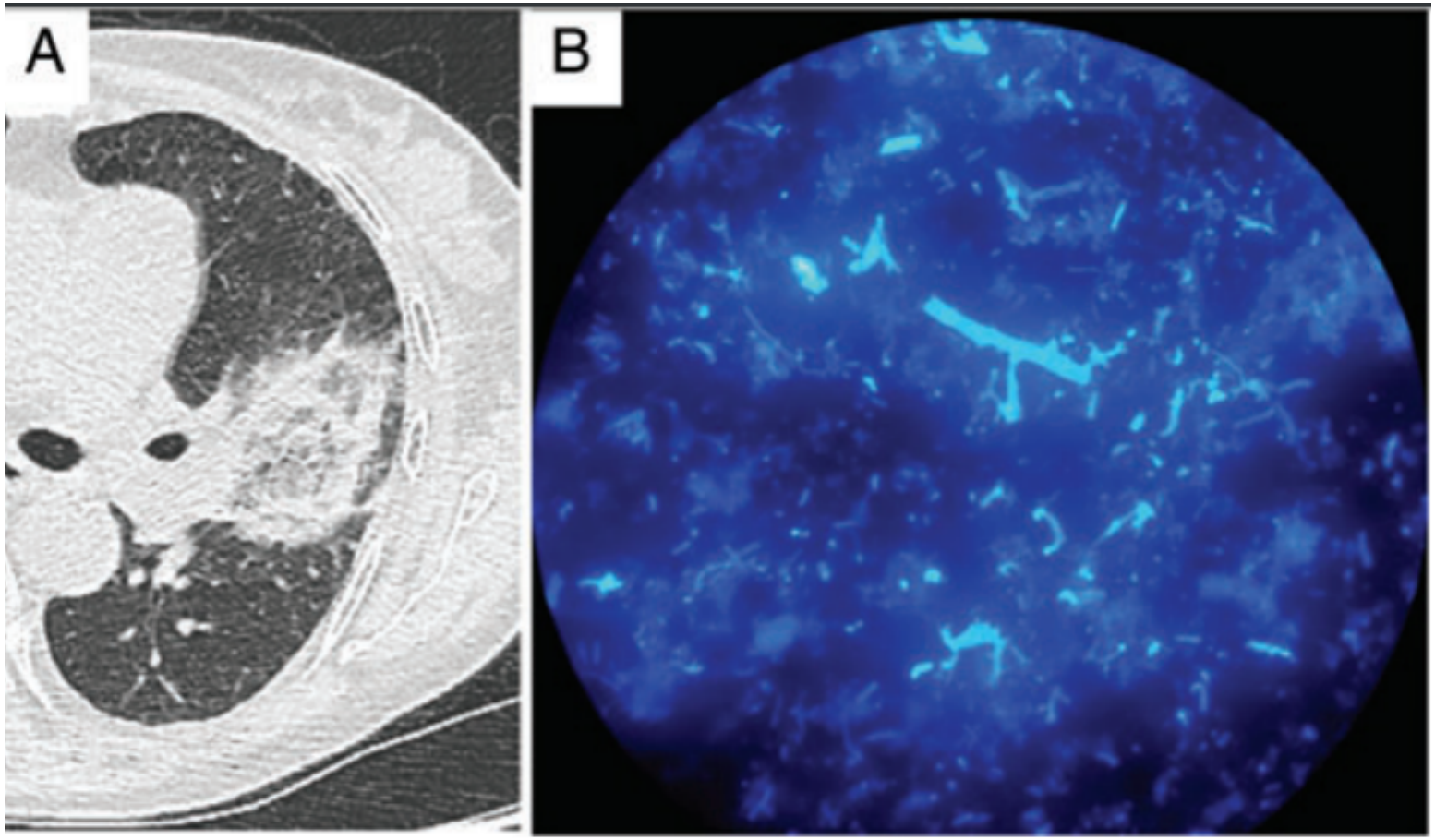
- not reliable as surveillance in asymptomatic pts on effective prophylaxis (results negative or FP)
- useful to diagnose pts with a clinical suspicion

Duarte CID 2014;

Galactomannan

negative in case of mucormycosis (as well as glucan)

Diagnosi: "reversed halo sign" may be suggestive



igure 1. Computed tomographic (CT) image and microscopic examina

Legouge et al, CID 2014

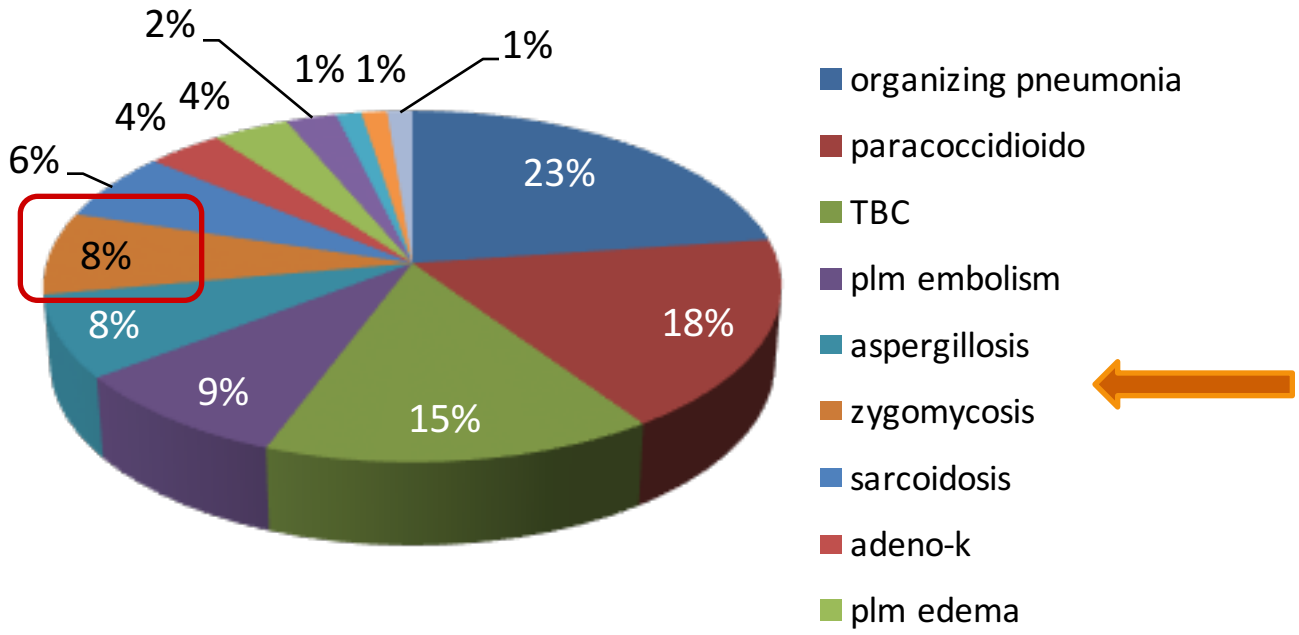
Official publication of the American College of Chest Physicians

CHEST PAPERS IN PRESS

2012

Reversed halo sign: high-resolution CT findings in 79 patients

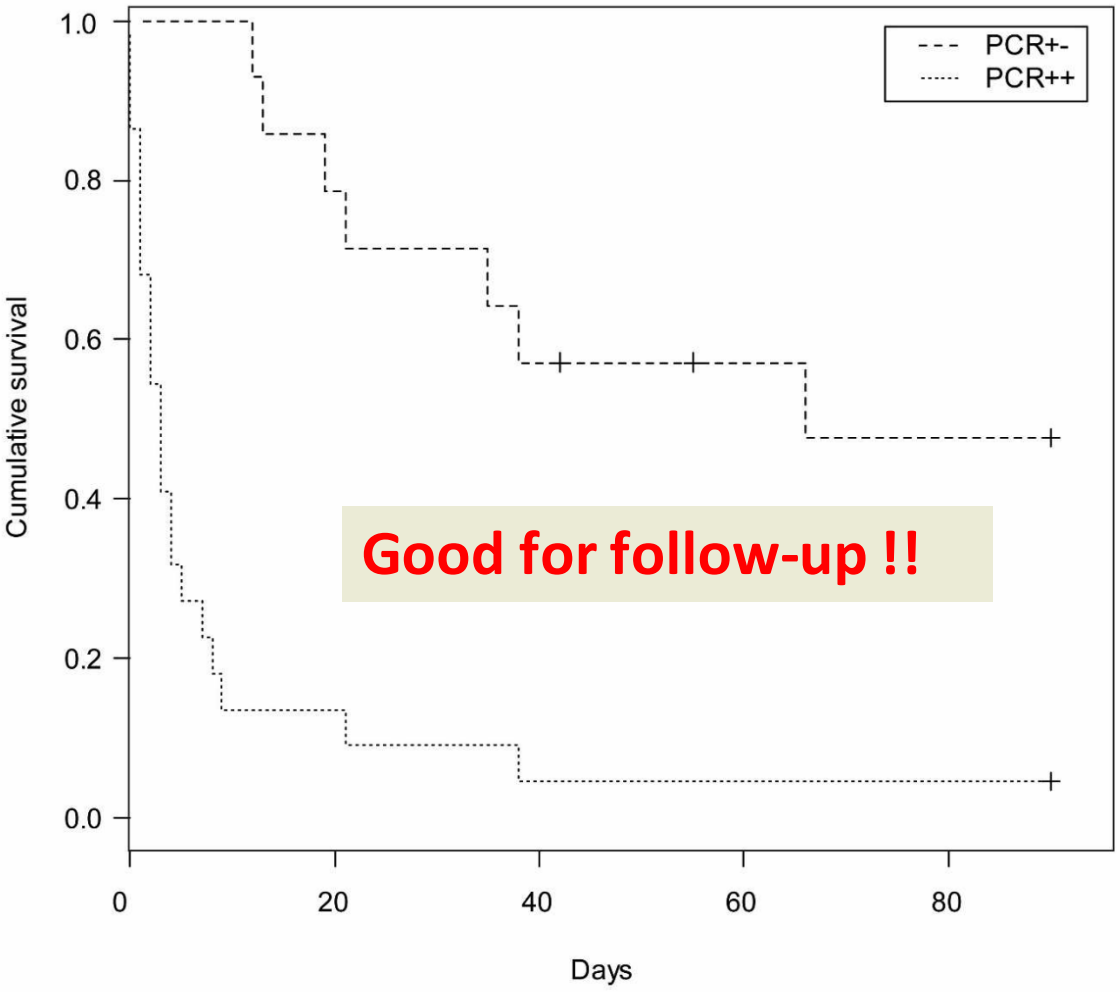
Edson Marchiori, Gláucia Zanetti, Dante Luiz Escuissato, Arthur Soares Souza, Jr, Gustavo de Souza Portes Meirelles, Joana Fagundes, Carolina Althoff Souza, Bruno Hochhegger, Edith M. Marom and Myrna B. C. Godoy



"RHS should be considered a relatively non specific sign"

Only 8% of reversed halo sign are in Mucormycosis

Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF).



Mucorales **qPCR not only could confirm the IM diagnosis when other 63 mycological arguments were present but also could anticipate this diagnosis. Quantification of 64 DNA loads may also be a useful adjunct to treatment monitoring**

Millon et al, CMI 2016

Open Forum Infectious Diseases

BRIEF REPORT

2016

Is It Time to Include CT "Reverse Halo Sign" and qPCR Targeting Mucorales in Serum to EORTC-MSG Criteria for the Diagnosis of Pulmonary Mucormycosis in Leukemia Patients?

Denis Caillot,[1,2] Stéphane Valot,[3] Ingrid Lafon,[1] Louise Basmaciyan,[3,4] Marie Lorraine Chretien,[1,2] Marc Sautour,[3,4] Laurence Million,[5,6] Caroline Legouge,[1,2] Alexandre Payssot,[1] and Frédéric Dalle[3,4]

[1]Department of Clinical Haematology, University Hospital, Dijon, [2]Inserm Unit 866, LabEx Team, Dijon School of Medicine, [3]Mycology and Parasitology Department, University Hospital, Dijon, [4]Bourgogne Franche-Comté University, Agrosup Dijon, UMR PAM, Team Vin, Aliment, Microbiologie, Stress, [5]Chrono-Environnement UMR, 6249 CNRS, Bourgogne Franche-Comté University, Besançon, and [6]Parasitology-Mycology Department, University Hospital, Besançon, France

In 23 leukemia patients with proven (n = 17) or possible (n = 6) pulmonary mucormycosis (PM), the presence of reversed halo sign on computed tomography was strongly associated with the positivity of quantitative polymerase chain reaction assays targeting Mucorales in the serum, confirming the value of these two tools for the diagnosis of PM in this setting.

Keywords. early diagnosis; leukemia; pulmonary mucormycosis; quantitative polymerase chain reaction; reversed halo sign.

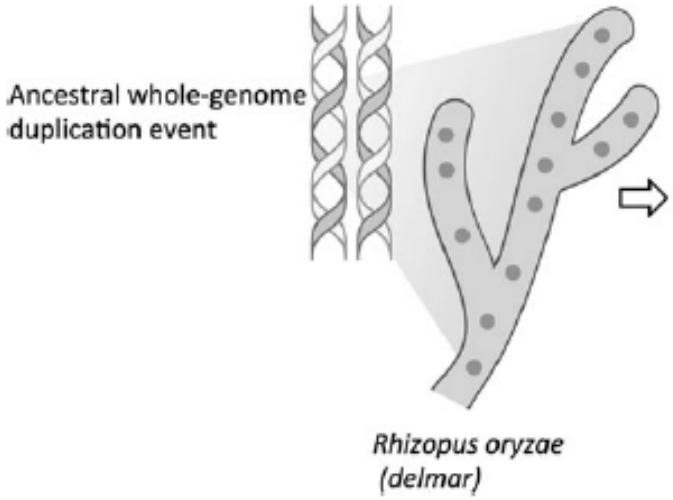
first-line treatment for invasive molds infections, and (iv) the lack of sensibility of noninvasive techniques for conventional diagnosis (ie, culture, direct examination), new tools were needed for the early and specific diagnosis of PM aimed at distinguishing PM from IPA to initiate appropriate therapy and improve the outcome of patients suffering from PM.

Recently, two publications provided attractive tools that could be useful in the specific diagnosis of PM in at-risk patients. First, a study by our team concluded that the reversed halo sign (RHS) on computed tomography (CT) scan was strongly associated with PM in the particular setting of neutropenic leukemia patients with pulmonary infections [6]. Second, Millon et al reported the usefulness of the screening of at-risk patients using specific quantitative polymerase chain reaction (qPCR) targeting circulating DNA of Mucorales in the serum for the early diagnosis of invasive mucormycosis [7]. The aim of the present study was to investigate the usefulness of combining CT scan and qPCR screening for the early diagnosis of PM in a retrospective series of neutropenic leukemia patients with proven or possible PM.

All of the patients included in this study were selected as previously described [6]. Briefly, leukemia patients with prolonged neutropenia (>10 days) who were treated for proven or possible PM between 2004 and 2014 at the Clinical Hematology Department, University Hospital of Dijon, France, based on the pres-

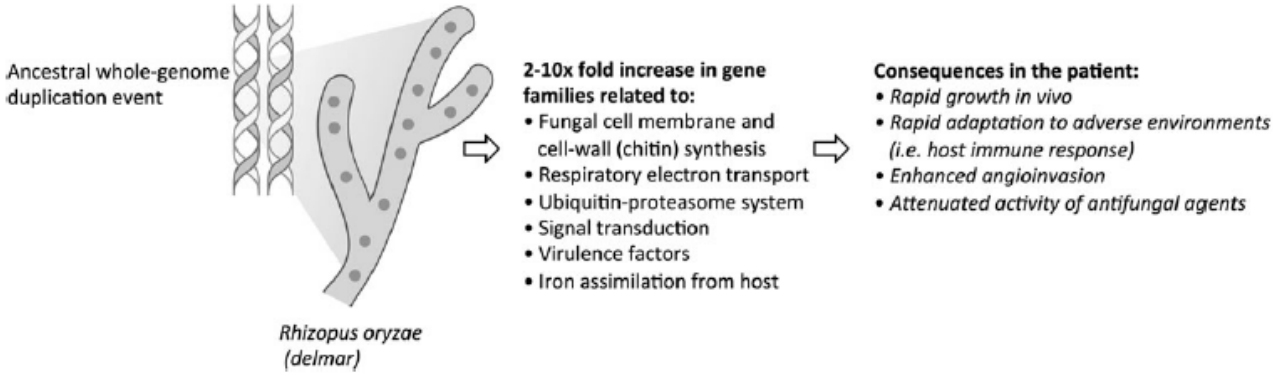
How Does Antifungal Pharmacology Differ for Mucormycosis Versus Aspergillosis?

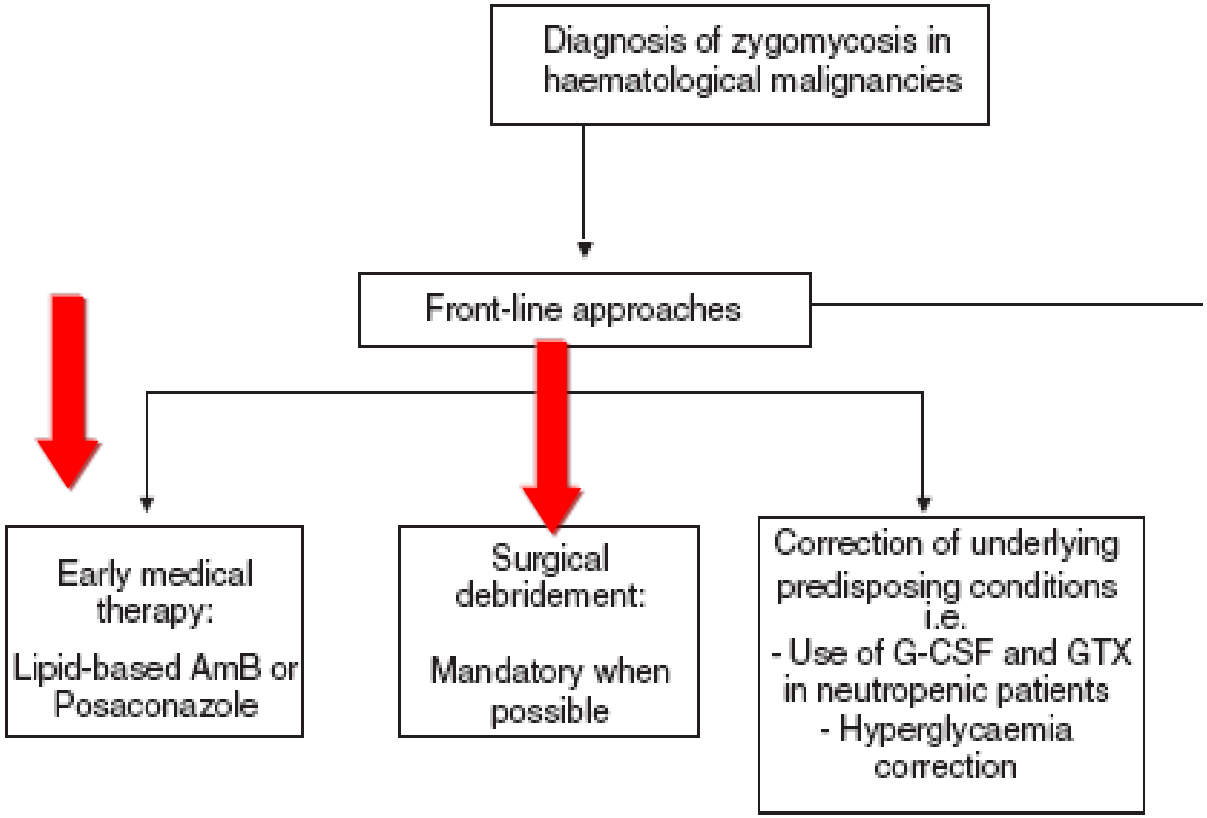
Russell E. Lewis,[1,5] Olivier Lortholary,[2] Brad Spellberg,[3] Emmanuel Roilides,[4] Dimitrios P. Kontoyiannis,[5] and Thomas J. Walsh[6]



- Ability to grow under varying conditions
- Production of several virulence factors (proteases, subtilase)
- Ability to accelerated synthesis and remodeling of membrane and cell wall –
- Assimilative capacity of the iron from Hb' host

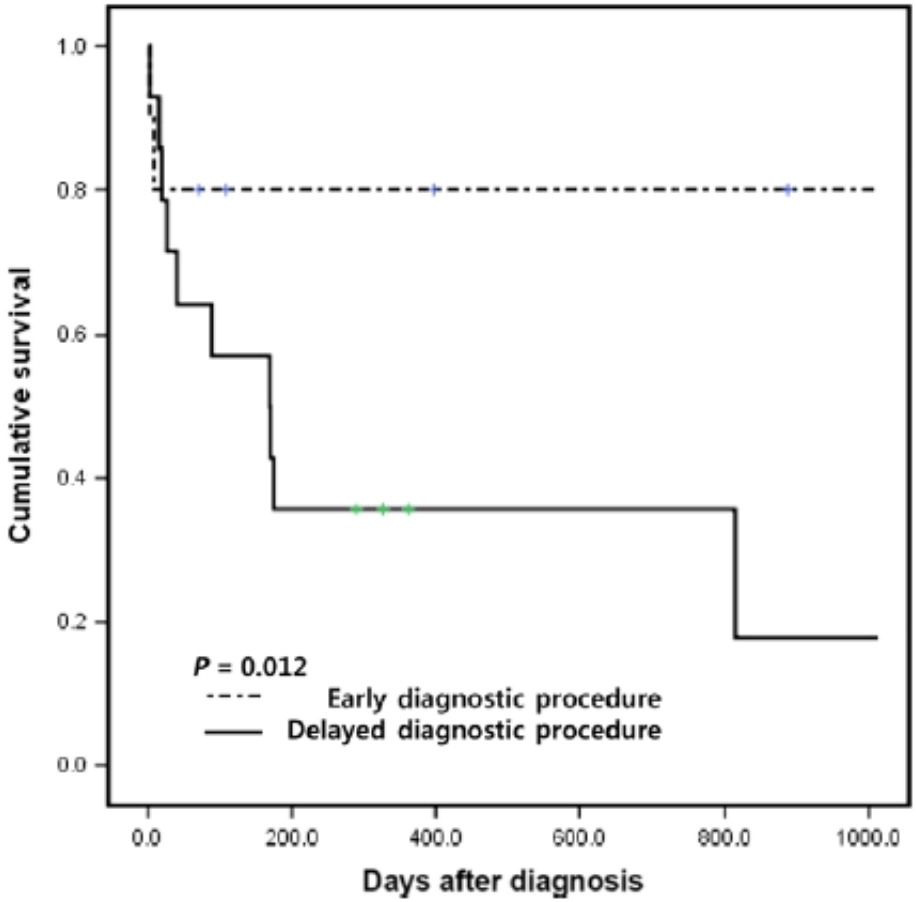
- Angio-invasive growth in humans
- Adaptability in hostile conditions
- Resistance to systemic antifungal therapies





Pagano et al., Br J Haematol 2009; 146(6):597-606

Delaying diagnostic procedure significantly increases mortality in patients with invasive mucormycosis



2005-2014
30 pts with proven/probable IM

	Odds ratio	95% CI	*P* value
Age	0.96	0.88–1.04	0.38
~~Renal failure~~	~~8.08~~	~~0.86–10.52~~	~~0.065~~
Delayed diagnostic procedure (≥16 days)	12.34	1.43–10.64	0.022

Jeong et al. Mycoses 2015

Factors influencing the course of Zygomycosis

Pagano et al, Haematologica 2004

Univariate analysis	P-value
Age	ns
Sex (M vs F)	0.033
Hematological disease	ns
Steroids use	ns
Hematological disease phase	ns
PMN recovery (yes vs no)	0.01
Infection site (lung vs other)	ns
AmB compounds vs other	0.01
L-AmB vs other treatments	0.001

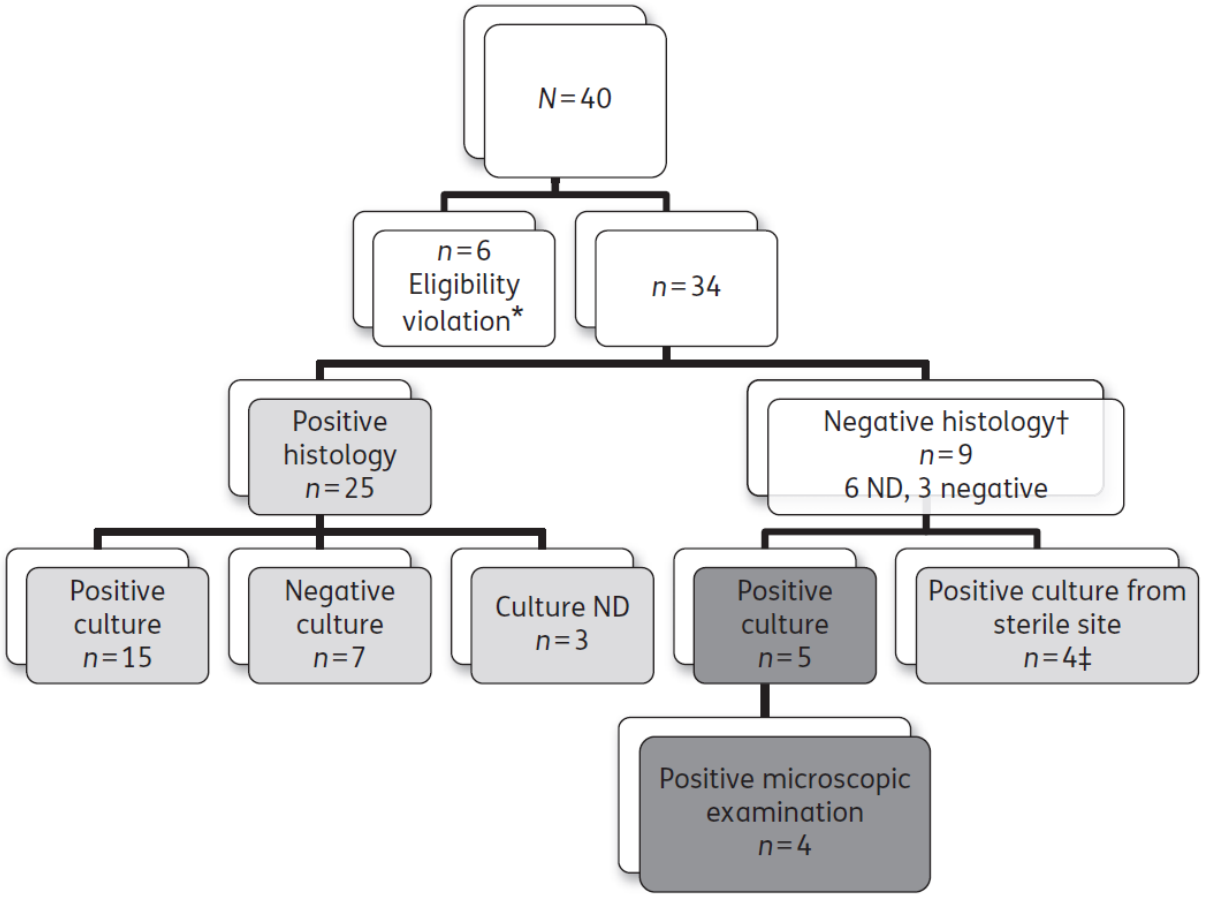
At a multivariate analysis only the treatment with L-AmB [RR=0.5 (CI 0.3-0.8; p=0.0001)] is significant

How is the better dose of L-AmB ?

- **3 mg/kg ?** *(Pagano et al, Haematologica 2004)*
- **3 → 5 mg/kg ?** *(Petrikkos et al, Eur J Clin Micr Infect Dis 2003)*
- **7.5 →15 mg/kg ?** *(Walsh et al, AAC 2001)*

Probably 5-7 mg/kg must be considered the better dosage

Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis



Patients' characteristics	
Male	21 (62)
Age (years)	53 (0.50–78.10
Time from symptom onset to treatment (days)	46 (4–344)
Underlying disease	
HM	18 (53)
haematopoietic stem cell	5/18 (28)
GVHD	3/18 (17)
neutropenia	6/18 (33)
corticosteroids	8/18 (44)
DM	6 (18)
trauma	3 (9)
solid organ transplant	3 (9)
other[a]	4 (12)
Site of infection	
lung	10 (29)
rhino-orbito-cerebral	9 (26)
skin	6 (18)
disseminated	6 (18)
other[b]	3 (9)

Lanternier et al. JAC 2015

Table 3. Treatment response according to Herbrecht and Segal criteria

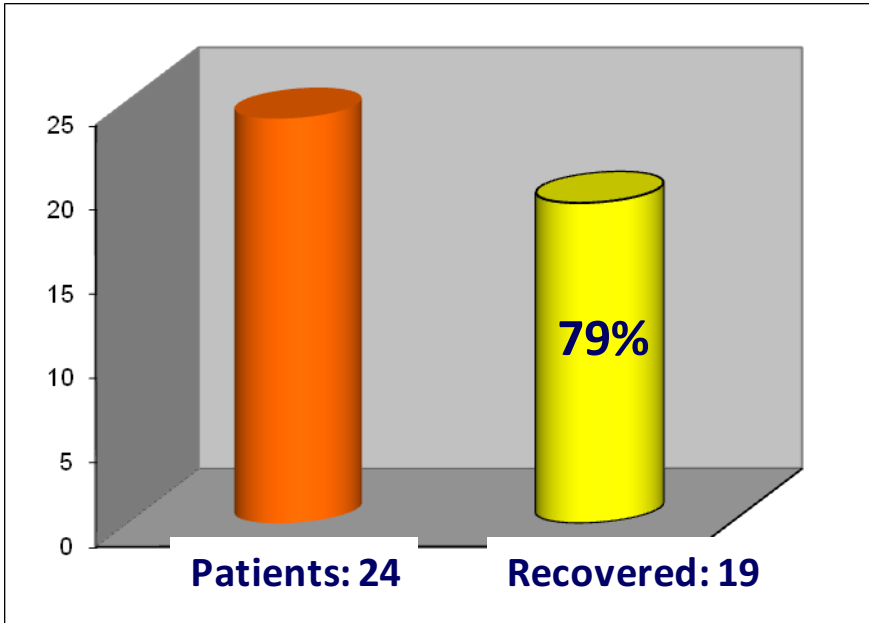
	Herbrecht, W4 or EOT if before ($n=33$)[a]	Segal, W4 or EOT if before ($n=32$)[b]	Herbrecht, W12 ($n=31$)[c]	Segal, W12 ($n=31$)[c]
Favourable response	12/33 (36%)	10/32 (31%)	14/31 (45%)	15/31 (48%)
partial response	6/33 (18%)	4/32 (13%)	4/31 (13%)	6/31 (19%)
complete response	6/33 (18%)	6/32 (19%)	10/31 (32%)	9/31 (29%)
Failure	21/33 (64%)	22/32 (69%)	17/31 (55%)	16/31 (52%)
stable	4/33 (12%)	7/32 (22%)	2/31 (6%)	1/31 (3%)
failure without death	10/33 (30%)	8/32 (25%)	2/31 (6%)	2/31 (6%)
death[d]	7/34 (21%)	7/34 (21%)	13/34 (38%)	13/34 (38%)
related to mucormycosis	5/34 (15%)		9/34 (26%)	
not related to mucormycosis	2/34 (6%)		4/34 (12%)	

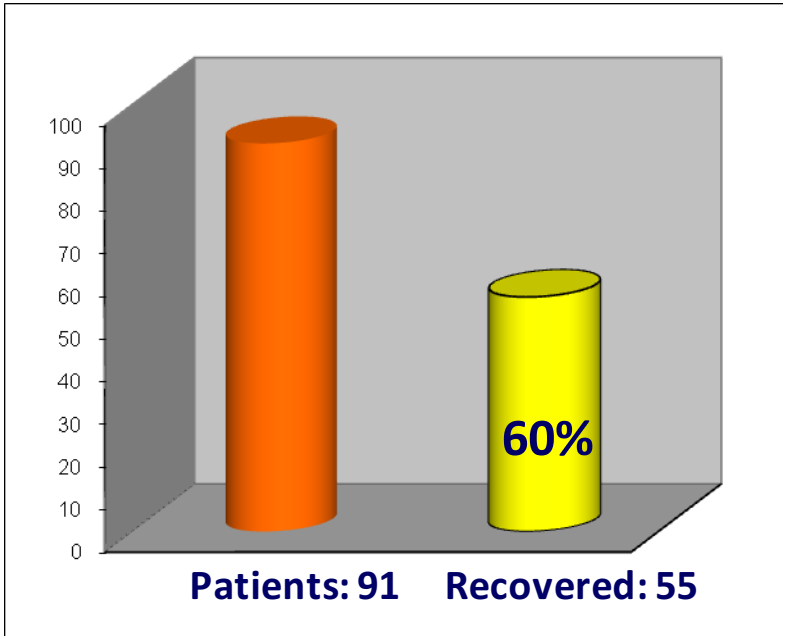
Table 4. Adverse events related to L-AMB

	No. (%)	Dose reduction	Treatment interruption	Definitive treatment interruption	Serious adverse events
Doubling of creatinine level[a]	16 (40)	7 (17)	5 (12)	1 (2)	4 (10)
Potassium level					
<2.5 mmol/L	2 (5)	0	0	0	1 (2)
<3 mmol/L[b]	16 (40)	1 (2)	0	0	2 (5)
Gastrointestinal	10 (25)	0	2 (5)	0	1 (2)
Rash	5 (12)	1 (2)	0	0	1 (2)
Elevation of liver enzymes[c]	4 (10)	1 (2)	1 (2)	0	0
Cholestasis	6 (15)	1 (2)	1 (2)	1 (2)	1 (2)
Lumbar pain					1 (2)
Hyperglycaem					1 (2)
Catheter thrombosis	1 (2)	0	0	0	1 (2)
Low blood pressure	3 (7)	0	0	0	0
Fever	3 (7)	0	1 (2)	0	0
Cytopenia	7 (17)	1 (2)	0	1 (2)	1 (2)

Fail to demonstrate a superior efficacy !!

Posaconazole in the treatment of proven/probable Mucormycosis





- All ref
- 11 rhi
- POS 8
- Durat

Two separate, but overlapping series of patients receiving posaconazole within compassionate use protocols of the manufacturer have been published

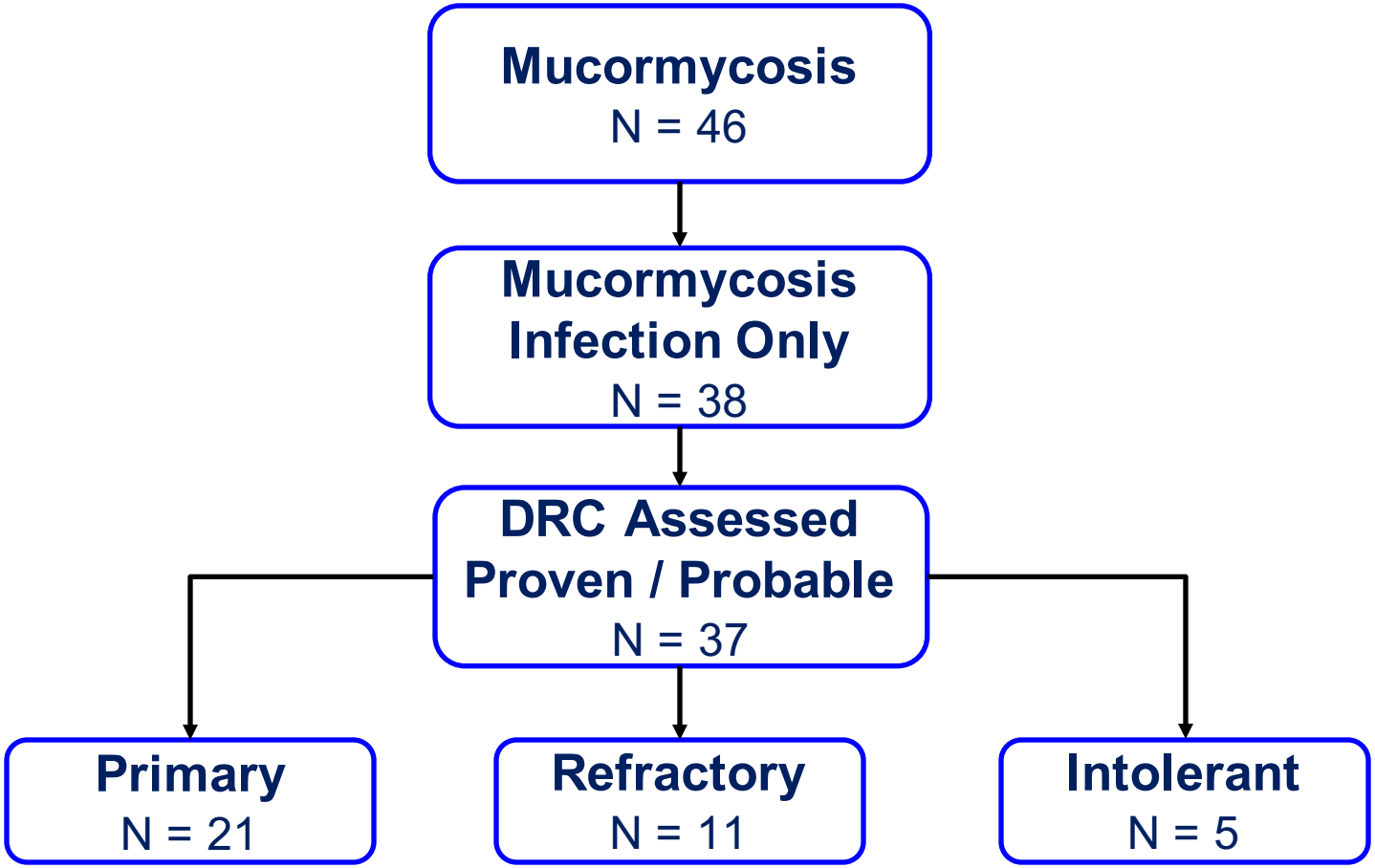
d

Greenberg et al, AAC 2006

Van Burik et al, CID 2006

Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis

Marty et al, Lancet Infect Dis 2016



Overall Response for Mucormycosis

Overall Response at EOT	Primary N = 21 %	Refractory N = 11 %	Intolerant N = 5 %	Total N = 37 %
Success	31.6	36.4	20.0	31.4
Complete	15.8	18.2	0	14.3
Partial	15.8	18.2	20.0	17.1
Failure	68.4	63.6	80.0	68.6
Stable	31.6	18.2	40.0	28.6
Progression	36.8	45.5	40.0	40.0

Marty et al, Lancet Infect Dis 2016

Combination Therapy for Mucormycosis: Why, What, and How?

Brad Spellberg,[1,2] Ashraf Ibrahim,[2,3] Emmanuel Roilides,[7] Russel E. Lewis,[4,5] Olivier Lortholary,[9,10] George Petrikkos,[8] Dimitrios P. Kontoyiannis,[5] and Thomas J. Walsh[6]

WHY?

The mortality rate of mucormycosis with monotherapy remains unacceptable

WHAT?

The proposed strategy should have shown:

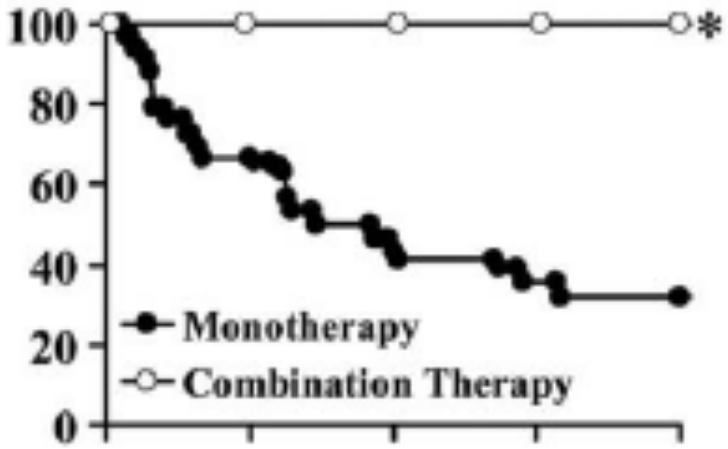
1) **Markedly improved survival in relevant animal models of IM.**
2) **Available retrospective or observational clinical data, concordant with preclinical models**
3) **Involvement of agents already approved for the use in humans**

Combination Polyene-Echinocandin in Rhino-Cerebral Zygomycosis

Reed et al. Clin Infect Dis 2008

- ✓ **12 Year Retrospective Review (37cases)**
- ✓ **Rhino-orbito-cerebral zygomycosis**
- ✓ Monotherapy with AmB formulation (31 patients) *versus* a combination of caspofungin and ABLC or L-AmB (6 patients)

	Proportion of patients (%)			Proportion of patients (%)			Proportion of patients (%)		
Patients	Monotherapy	Combination therapy	*P*	ABLC	AmB or LAmB	*P*	ABLC	ABLC plus caspofungin	*P*
Evaluable	14/31 (45)	6/6 (100)	.019	7/19 (37)	13/18 (72)	.029	3/15 (20)	4/4 (100)	.009
All	14/34 (41)	6/7 (86)	.040	7/22 (32)	13/19 (68)	.018	3/17 (18)	4/5 (80)	.021
With CNS disease	4/16 (25)	4/4 (100)	.015	3/12 (25)	5/8 (63)	.113	1/10 (10)	2/2 (100)	.047



Pts receiving COMBO had a significantly higher response rate and survival

LIMITS: LOW NUMBER
most of pts had diabetes
rhinocerebral forms only
all had surgery

Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007

Skiada et al, CMI 2011

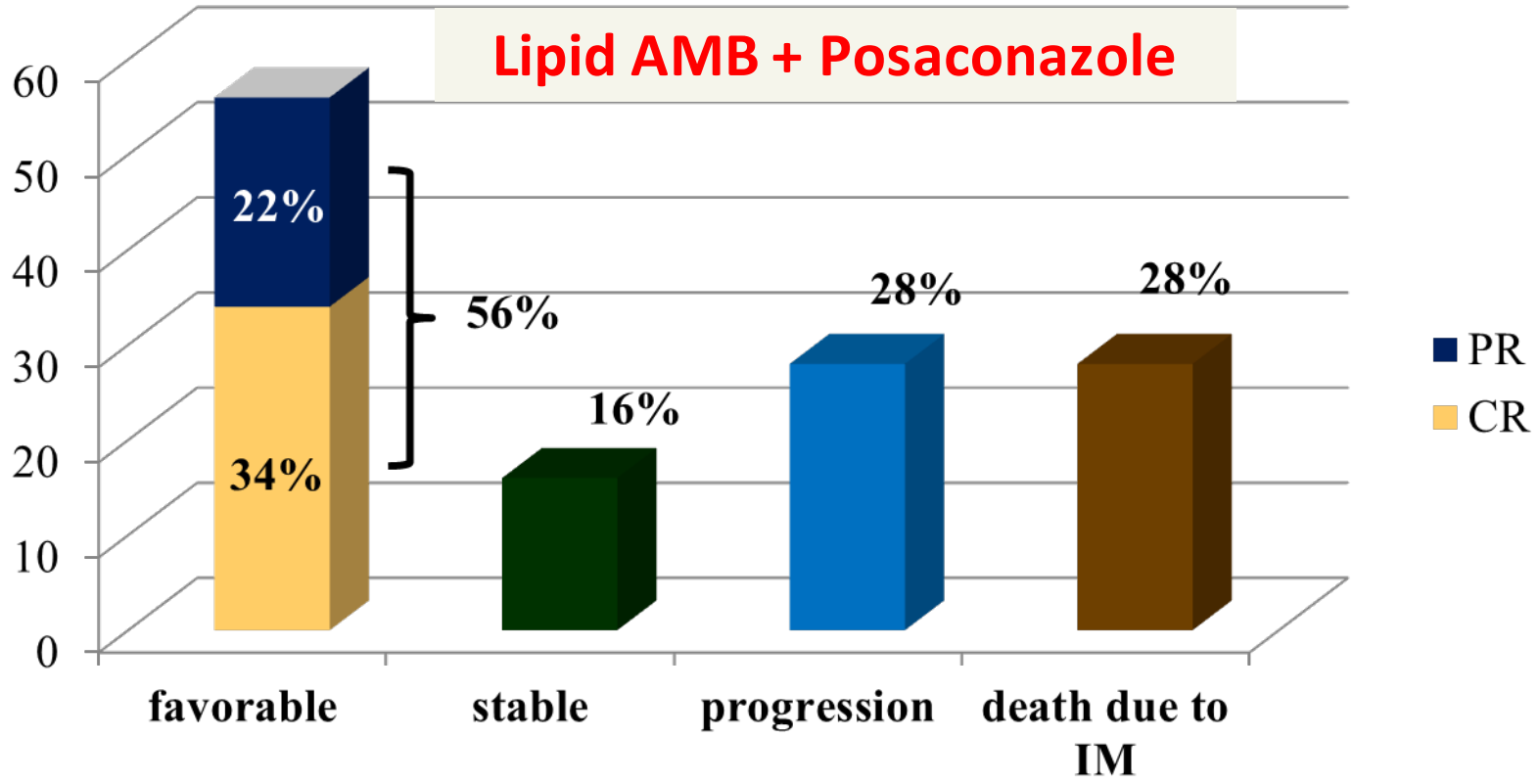
Amphotericin B alone[b]	90 (39)		32/82 (39)
d-AmB	12/90 (13)		6/12 (50)
L-AmB	68/90 (76)		20/62 (32)
ABLC	4/90 (4)		2/4 (50)
Unspecified ampho B	6/90 (7)		4/4 (100)
Amphotericin B + posaconazole[b]	48 (21)		13/43 (30)
Amphotericin B + Posa + other[c]	13 (6)	34%	2/11 (18)
Amphotericn B + other[c]	16 (7)		11/16 (69)

[b]Posaconazole was administered either in combination with (18 cases, 38%) or sequentially following amphotericin B treatment (28/48 cases, 58%). In two cases it was unclear whether they were given in combination or sequentially. The formulation of amphotericin B used was liposomal amphotericin B in 43 cases (90%).

[c]Caspofungin, itraconazole, voriconazole, fluconazole.

Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematologic diseases: a report from the SEIFEM and FUNGISCOPE registries

Pagano et al, Haematologica 2013

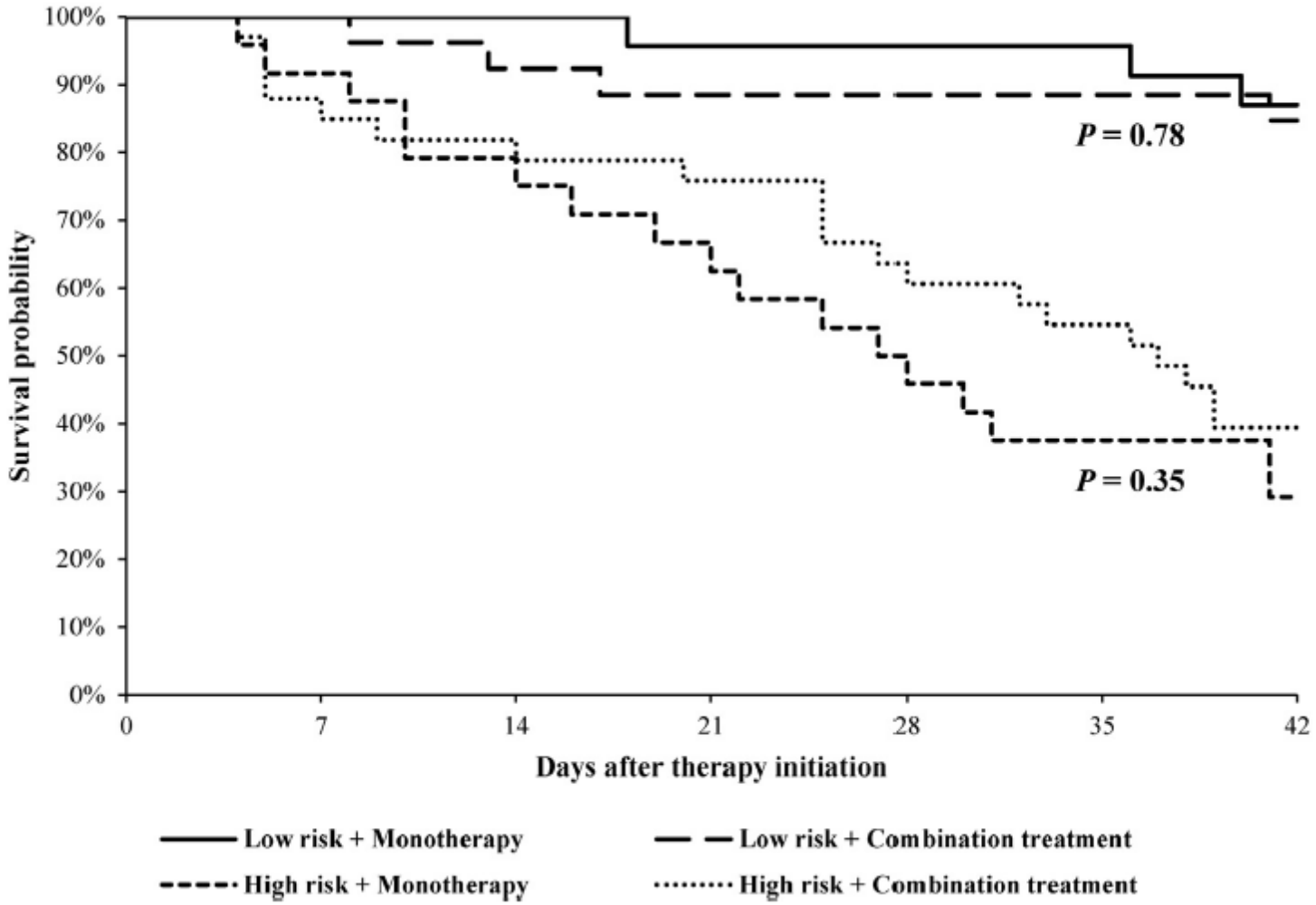


32 patients, 8 of them allo-HSCT (25%), not responsive to monotherapy and with an advanced disease

Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis

Clinical Microbiology and Infection 22 (2016)

A. Kyvernitakis [1, 2], H.A. Torres [1], Y. Jiang [1], G. Chamilos [3], R.E. Lewis [4], D.P. Kontoyiannis [1, *]



Surgery and Mucormycosis

Surgery	Yes Death/treated	No Death/treated
Mortality in ECMM Study **230 cases**		
Surgical treatment related to decreased mortality (Odds ratio 0.21, 95% CI 0.09-0.48, p=0.001) *Skiada et al, CMI 2011*		
Petrikkos et al, Eur J Microbiol Infect Dis 2003	6/17	7/7
Sims et al, Arch Med Res 2006	2/12	2/4
Total	**13/73 (17%)**	**73/98 (74%)**

EMERGENCY AND ELECTIVE PULMONARY SURGICAL RESECTION IN HAEMATOLOGICAL PATIENTS WITH INVASIVE FUNGAL INFECTIONS: A REPORT OF 50 CASES IN A SINGLE CENTRE

	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%)**
Haematological responses and outcome			
Patients achieving haematological CR	21 (78%)	18 (78%)	**39 (78%)**
Patients receiving new haematological therapy after surgery	25 (93%)	19 (83%)	**44 (88%)**
Survival at 1 month post surgery	25 (93%)	22 (96%)	**47 (94%)**
Survival at 3 months post surgery	24 (89%)	21 (91%)	**45 (90%)**
Survival at 6 months post surgery	21 (78%)	18 (78%)	**39 (78%)**

Chretien et al., CMI 2015

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

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

Population	Intention	Intervention	SoR	QoE	Comment	References
Any	To increase survival rates	Surgical debridement	A	IIu	*n* = 32	120
					n = 90	3
					n = 45	38
					n = 9	7
					n = 59	25
					n = 92, paediatric	121
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	IIu	*n* = 470	3
					n = 19	122
					n = 90	7
					n = 92, paediatric	121
Immunocompromised	To increase survival rates	Immediate treatment initiation	A	IIu	*n* = 70	27
Any	To cure and to increase survival rates	Amphotericin B, liposomal ≥5 mg/kg[a]	A	IIu	*n* = 4	105
					n = 16	196
					n = 5	128
					n = 21	26
					n = 28	152
					n = 130	7
					n = 40	57
					Animal model	124
					Animal model	125
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days[a]	A	II	Animal model	127
					Animal model	126
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg[a]	B	IIu	*n* = 10	130
					n = 7	7
					Animal model	126
					Animal model	127
Any	To cure	Posaconazole 4 × 200 mg/day or 2 × 400 mg/day[a]	B	IIu	*n* = 8	26
					n = 17	7
					Animal model	131
Any	To cure	~~Lipid-based amphotericin plus caspofungin[a]~~	~~C~~	~~III~~	*n* = 7	135
Any	To cure	Amphotericin B, deoxycholate, any dose[a]	D	I	Renal toxicity	137
					n = 9	105
					n = 532	3
					Renal toxicity	136
					n = 10	38
					n = 21	7

Tortorano et al, CMI 2014.

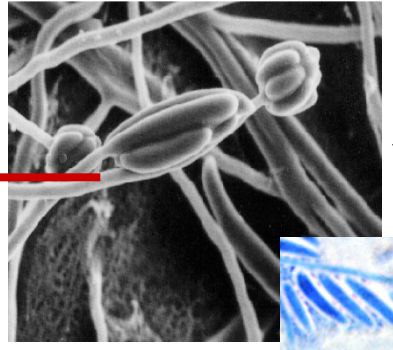
TABLE 13. Recommendations for mucormycosis in solid organ transplant recipients

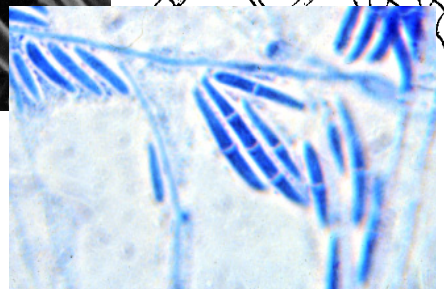
Population	Intention	Intervention	SoR	QoE	Comment	References
Solid organ transplantation	To cure	AmB lipid formulation	A	IIh	$n = 25$ $n = 14$, pulmonary $n = 3$	178 177 25
Solid organ transplantation	To cure	Surgery	A	IIu	$n = 11$, pulmonary $n = 10$, sinu-nasal-cerebral	177 179

QoE, quality of evidence; SoR, strength of recommendation.

Tortorano et al, CMI 2014.

Fusarium spp.





- Plant pathogen, soil saprophyte
- Inalation, ingestion, direct inoculation
- Includes *F.solani* (50% isolates), *F.moniliforme*, *F.oxysporum*

A wide spectrum of clinical manifestations

Due to a device

- cheratitis by contact lens
- CVC related infection

Single organ infection

- cheratitis, endophtalmitis
- onicomicosis

Disseminated

(immunocompromised pts)

- FUO
- skin
- lung/sinusitis
- sepsis
- cellulitis
- CNS

Fusarium versus *Aspergillus*

		FUSARIOSIS
CLINICAL FEATURES	Persitent fever	√
	Sinopulmonary infection	√
	Skin lesions	√ **50-70%**
	Myalgias	√
RADIOLOGY	Subpleural opacity	√
	Cavitation	√
HISTO-PATHOLOGY	Angioinvasion	√
	Acute branching septate hyphae	√
MICROBIOLOGY	Positive blood coltures	√ **50-70%**
	1,3-β-D-glucan	√

Invasive and disseminated fusariosis

HSCT (mainly allogeneic)

ITALY	0.2%	(SEIFEM, Pagano et al CID 2007)
USA	3%	(TRANSNET, Kontoyiannis et al CID 2010)
BRAZIL	2%	(9 centers; Nucci et al CID 2004)
BRAZIL	5.2%	(8 centers; Nucci et al CMI 2013)

Acute myeloid leukemia

ITALY	0.4%	(SEIFEM, Pagano et al Haematologica 2006)
BRAZIL	3.8%	(8 centers; Nucci et al CMI 2013)

Solid organ transplant

very rare (mainly in lung recipients; Carneiro et al Medicine 2011)

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

Diagnosis of fusariosis

★ Chest CT: **A III**

Non specific

Marom AJR 2008

★ Direct microscopy: **A III**

Non specific. Positive direct microscopy supports growth in culture

★ Histopathology: **A III**

angle branching hyphae similar to those of *Aspergillus*

Guarnier CMR 2011

★ Culture: **AIII**

Isolation of *Fusarium* in culture needed for a definitive diagnosis in presence of hyphae in tissue

Fusarium spp. easily recovered on routine mycological media without cycloheximide.

Caution in interpretation of growth (possible contamination)

Blood cultures have a high yield .

Easily isolated from skin biopsy (frequent metastatic skin lesions)

Tortorano et al, CMI 2014.

In vitro susceptibility of *Fusarium spp.*

TABLE I. Overview of possible *in vitro* antifungal susceptibility patterns for selected hyalohyphomycetes

Pathogen	AMB	Flucytosine	Echinocandins	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Fusarium solani	I-R	R	R	R	R	S-I-R	S-I-R
Scedosporium apiospermum	I-R	R	S	I-R	S-R	S	S
Scedosporium boydii	I-R	R	S	I-R	S-R	S	S
Scedosporium aurantiacum	R	NT	R	NT	R	S	S-R
Scedosporium prolificans	R	R	S-I-R	R	R	R	R
Paecilomyces species	S	I	R	R	S	I-S	S
Purpureocillium liliacinum	R	R	R	R	S	S	S
Acremonium species	S-R	R	R	R	S-R	S-R	S-R
Scopulariopsis species	I-R	R	NT	R	R	R	I-R

INACTIVE

- 5- Flucytosine
- Ketoconazole
- Fluconazole
- Itraconazole
- Caspofungin
- Anidulafungin/Micafungin

ACTIVE

AmB and lipid formulations

- Voriconazole
- Posaconazole/Ravuconazole
- Terbinafine
- AmB + Rifampicine
- AmB + Azithromycin

Tortorano et al, CMI 2014.

TABLE 5. Summary of recommendations for treatment of *Fusarium* infection

Population	Intention	SoR	QoE	Comment
Immunocompromised patients	First-line treatment			
	Voriconazole	A	IIt,r	Therapeutic drug monitoring required Response rate was associated with underlying condition and infection site
	Liposomal amphotericin B	B	IIt,r	Fungi may be resistant to amphotericin B
	Amphotericin B lipid complex	C	III	Limited case reports
	Amphotericin B deoxycholate	D	IIt,u	Fungi often resistant to amphotericin B Breakthrough infections may occur Excessive toxicity
	Any echinocandin	D	III	Intrinsically resistant
	Any combination therapy	C	III	Limited reports Combination not better than voriconazole alor
	Salvage treatment			
	Posaconazole	A	II	Overall success rate 50% Breakthrough infections Therapeutic drug monitoring required
	Voriconazole	A	III	Substantial efficacy Therapeutic drug monitoring required

Tortorano et al, CMI 2014.

International Retrospective Analysis of 73 Cases of Invasive Fusariosis Treated with Voriconazole▽

Olivier Lortholary,[1,2] Gaelle Obenga,[1] Pinaki Biswas,[3] Denis Caillot,[4] Elisabeth Chachaty,[5] Anne-Lise Bienvenu,[6] Muriel Cornet,[7] John Greene,[8] Raoul Herbrecht,[9] Claire Lacroix,[10] Frédéric Grenouillet,[11] Issam Raad,[12] Karine Sitbon,[1] Peter Troke,[13]* and the French Mycoses Study Group†

AAC 2010

78% with HMs
Overall 90-day survival **42%**

- primary = salvage therapy
- vori alone = combo

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)	

Fusariosis outcome in HMs

Study (years)	Drug in study	Cases (n)	Favorable outcome, n (RR)
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%)
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%)

52% (45-82%) in clinical trials

42% (6-79%) in case series

Caira *et al*, Expert Rev Antinfect Ther 2011

Improvement in the outcome of invasive fusariosis in the last decade

Nucci et al, CMI 2014

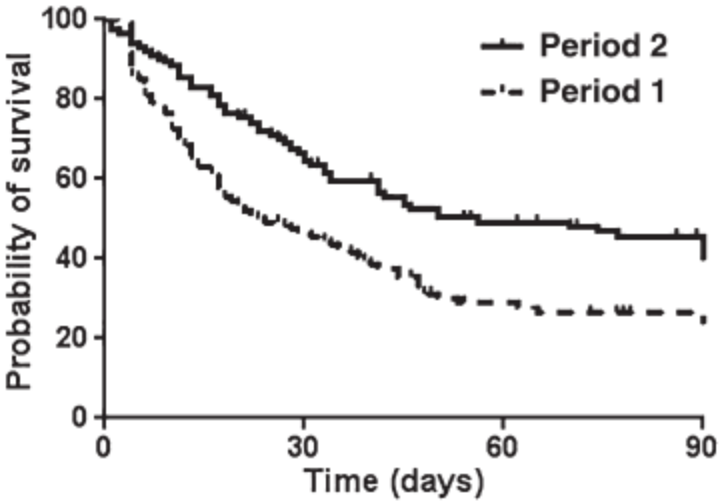
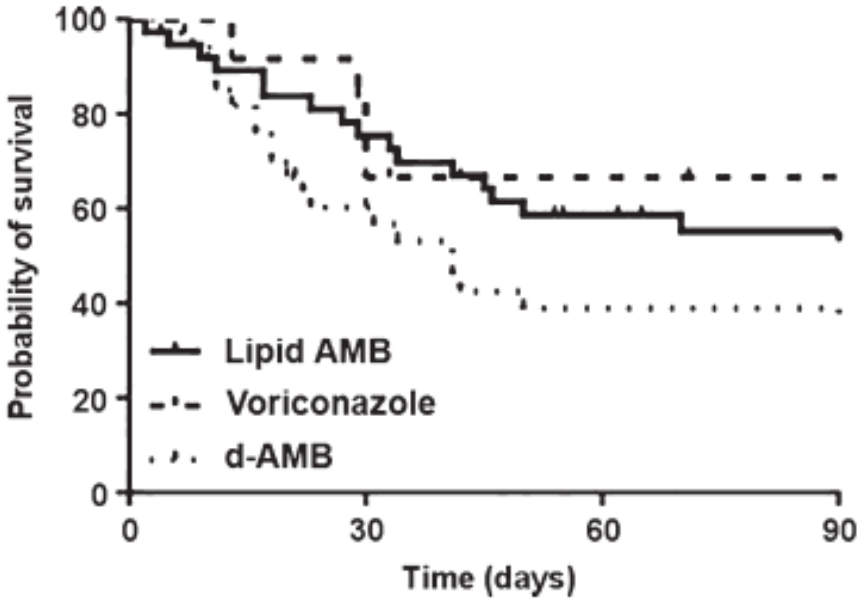


FIG. 1. Probability of 90-day survival of 233 patients with invasive fusariosis in period 1 (1985–2000) and period 2 (2001–2011).



Treatment of *Fusarium* infections

First line treatment of disseminated infection in immunocompromised pts

★ Voriconazole: **A II** IV: 6mg/Kg BID (1 day); 4mg/Kg BID (3 days) Oral: 200mg BID	47% complete/partial response TDM required	Perfect CID 2003 Campo J Inf 2010 Lortholary AAC 2010
★ Liposomal AMB: **B II** ★ AMB lipid complex: **C III** ★ Conventional AMB: **D II**	*Fusarium* may be resistant to AMB High dosage required	Nucci Cancer 2003 Jensen CMI 2004 Musa BrJHaemat 2000 Patterson Clin Ped 1996
★ Echinocandins: **D III**	*Fusarium* intrinsically resistant	Nucci CID 2004
★ Any combination: **C III**	Unclear results	Campo J Inf 2010 Lortholary AAC 2010

Treatment of *Fusarium* infections

Second line treatment of disseminated infection in immunocompromised pts

★ Posaconazole: **A II**

200mg QID or 400mg BID

48% complete/partial response

Breakthrough infections during prophylaxis

TDM required

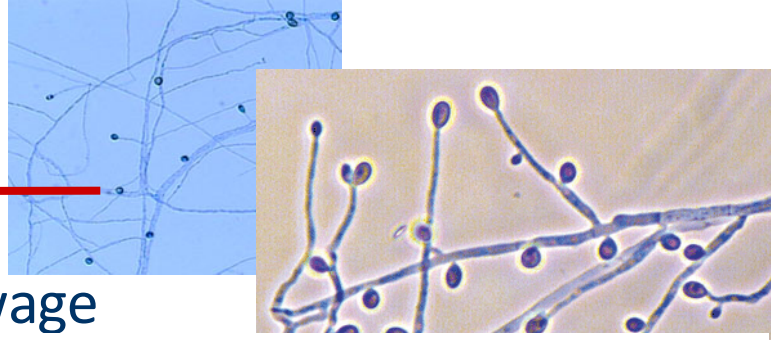
Raas CID 2006
Campo J Inf 2010

★ Voriconazole: **A III**

TDM required

Baden Transplantation 2003

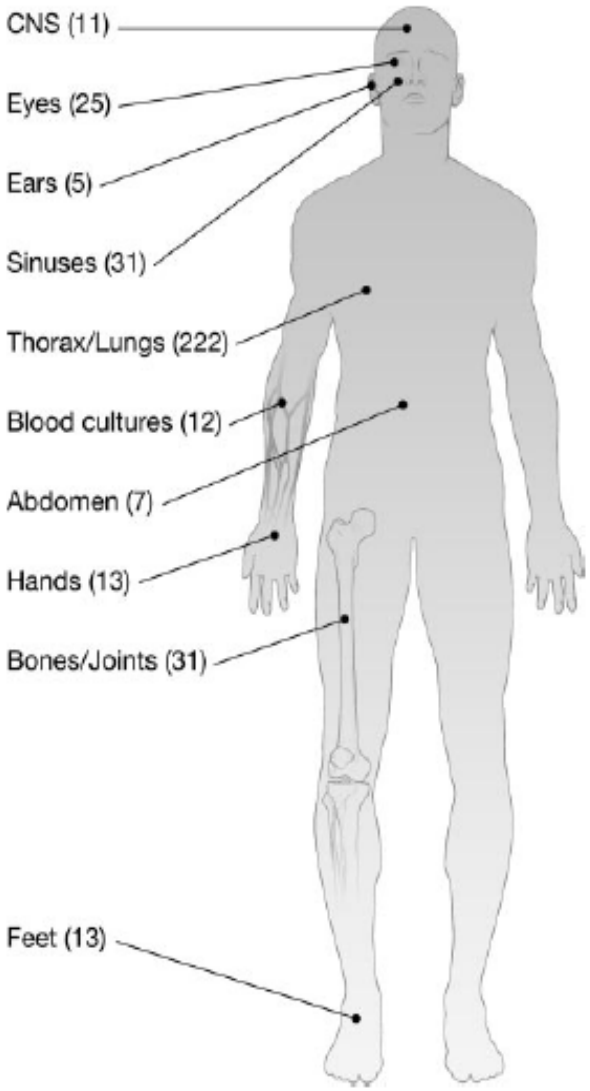
Scedosporium spp.



- Isolated from soil, polluted water or sewage
- Comprises two species: ***S. prolificans*** and ***S. apiospermum*** [Pseudallescheria boydii (ar apiospermum)]

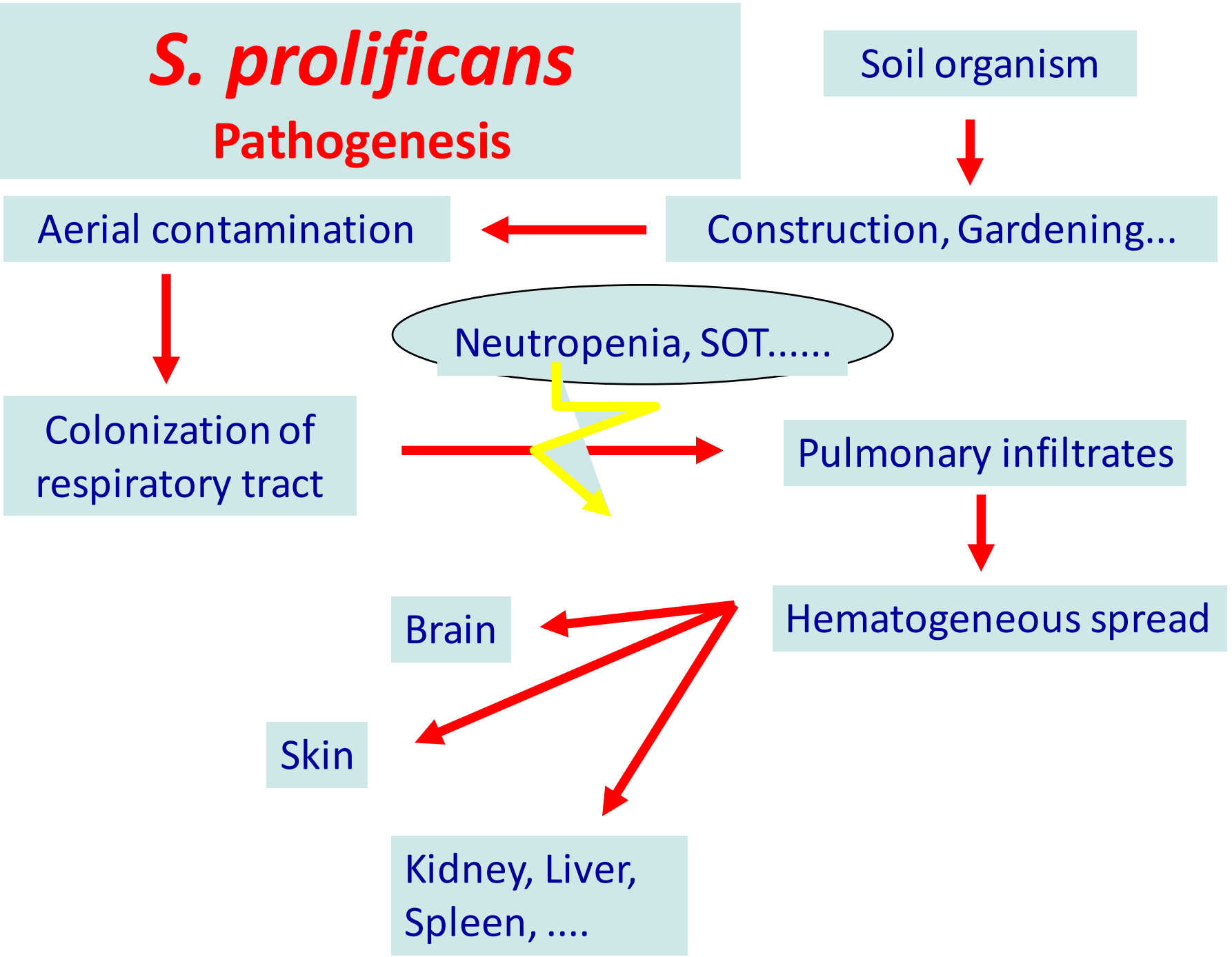
- Clinical features are extremely variable
- Clinical forms and outcome strictly relate to immune status

370 cases of *Scedosporium* spp. in Texas 2000-2007



Cortez et al, Clin Microbiol Rev 2008;21(1):157-197

S. prolificans
Pathogenesis



S.prolificans vs *apiospermum*

	S.PROLIFICANS	S.APIOSPERMUM
EPIDEMIOLOGY	**Rare** **Spain and Australia**	**More frequent** **Worldwide**
1st CASE REPORTED	1984: osteomyelitis	1898: Madura foot
RISK FACTORS	Neutropenic > immunocompetent	>> neutropenic pts
CLINICAL FORMS	Mycetoma, eye, osteoarticular, lung, CNS, skin infections	Mycetoma, osteomyelitis, eye, sinus, lung, CNS infections
DIAGNOSIS	**Blood cultures frequently positive**	Rarely positive
OUTCOME (AMR)	**85-100%**	65-75%
***IN VITRO* SUSCEPTIBILITY**	**Broad spectrum resistance**	**Voriconazole and posaconazole. Resistance to Amb and echinocandins**

Laboratory diagnosis of *Scedosporium* infections

★ Direct microscopy: **A III**

Non specific. Positive direct microscopy supports growth in culture

★ Histopathology: **A III**

Non specific. Hyaline septate acute angle branching hyphae similar to those of other hyalohyphomycetes

★ In situ hybridization: **C III**

Reagents not commercially available
Techniques not validated
Low sensitivity for *Pseudallescheria/Scedosporium*

Hayden Diagn Mol Pathol 2003
Montone AmJClinPathol 2009

TABLE 8. Summary of recommendations for treatment of *Scedosporium* spp. infections

Population	Intention	SoR	QoE	Comment
Immunocompromised patients	First-line treatment			
	Voriconazole	A	IIr,t	Therapeutic drug monitoring required Success in 66%
	Itraconazole	D	III	Only one case, failed
	Any combination	C	III	Unclear whether combination is more effective than either drug alone
	Liposomal amphotericin B	C	III	Variable activity
	Amphotericin B deoxycholate	D	III	*S. apiospermum* may be resistant Excessive toxicity
	Posaconazole	C	III	Only case reports

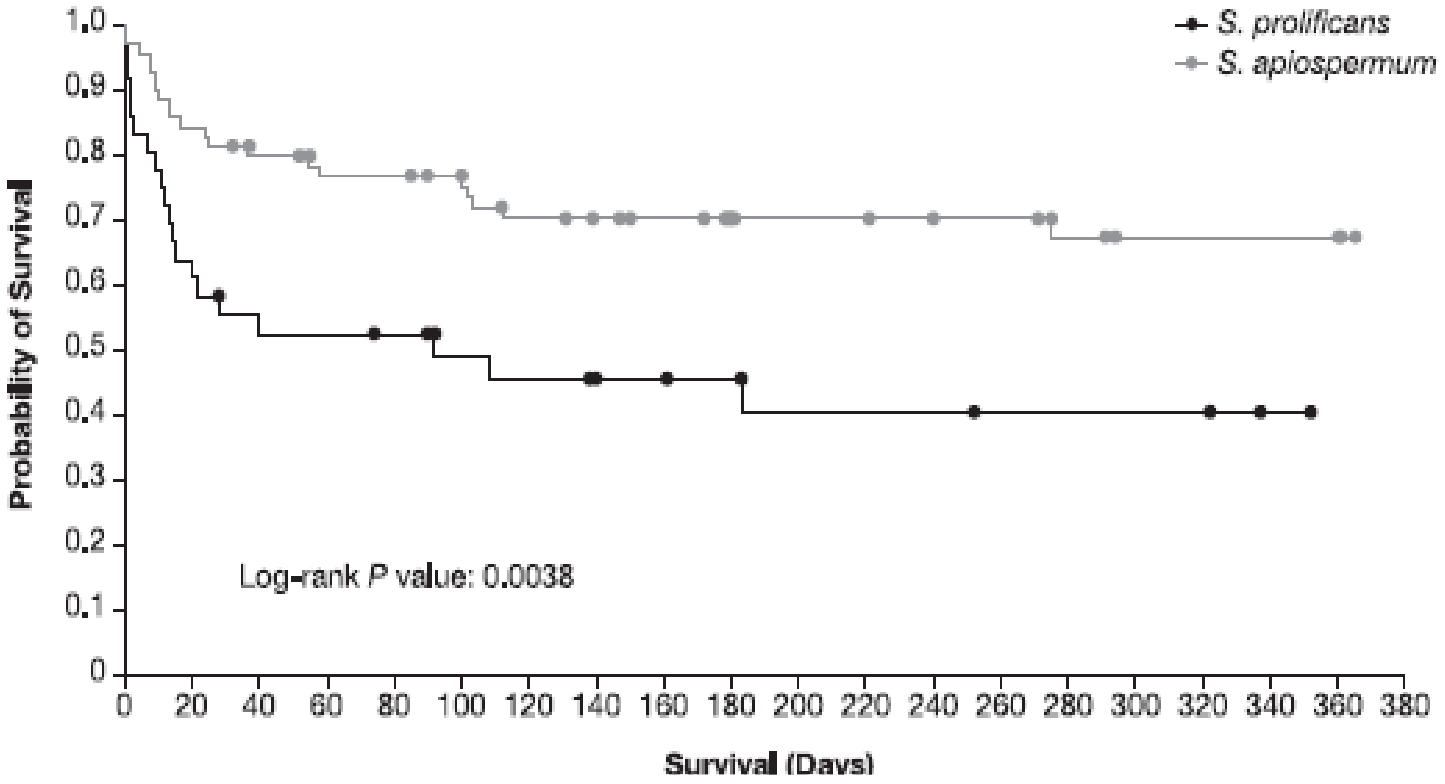
Tortorano et al, CMI 2014.

Voriconazole in scedosporiosis

107 cases of patients treated with voriconazole

Overall Response: 57%

Ranging from **91%** for skin localization to **29%** for uncommon sites (orbite,orecchio,corde vocali)



Troke et al, Antimicrob Agents Chemother 2008;52(5):1743-50.

Treatment of *Scedosporium* infections in pts with cerebral abscess

First line treatment

★ Voriconazole: **A III**	Good CNS penetration Surgery if possible	Buzina MM 2006 Chakraborty Jneurosurg 2005 Leechawengwong Mycoses 2007

Second line treatment

★ Combined therapy (Posa+LAmB; Caspo+Vori): **C III**	Case reports

Treatment of *Scedosporium prolificans* infections

Disseminated or pulmonary in immunocompromised pts

★ Voriconazole: **B II**	40% survival rate	Husain CID 2005 Nishio KansenshogakuZasshi 2012 Troke AAC 2008

Pulmonary infection in immunocompromised pts

★ Vori/Posa+Terb: **B III**	50% (3/6) survival	Case reports
★ Itraconazole: **C III**	15% (3/12) survival	Case reports
★ Amphotericin B: **D III**	4% (1/26) survival	Case reports

TABLE 10. Indications for surgical removal of tissue infected with *Fusarium* and *Scedosporium* species

Surgical intervention	SoR	Qoe	References
Haemoptysis from a single cavitary lung lesion (always perform a computerized chest scan to search for other lesions)	A	III	[2,5,57–59]
Progressive cavitary lung lesion (always perform a computerized chest scan to search for other lesions)	A	III	[2,5,57–59]
Infiltration into the pericardium, great vessels, bone or thoracic soft tissue	A	III	[2,5,57–59]
Osteomyelitis, septic arthritis	A	IIr	[2,46,47,155–159,257,287]
Resection of infected/colonized tissue before commencing immunosuppressive agents to prevent dissemination in case of cytotoxic therapy	A	III	[2]

QoE, quality of evidence; SoR, strength of recommendation.

Tortorano et al, CMI 2014.

Conclusions

- Difficulties in identifing more uncommon fungal agents
- High rate of unidentified etiologic agents
- Little experiences
- Increasing proportion of high risk patients

Knowledge of epidemiology and susceptibility appear to be crucial to define optimal empirical and/or pre-emptive antifungal treatments

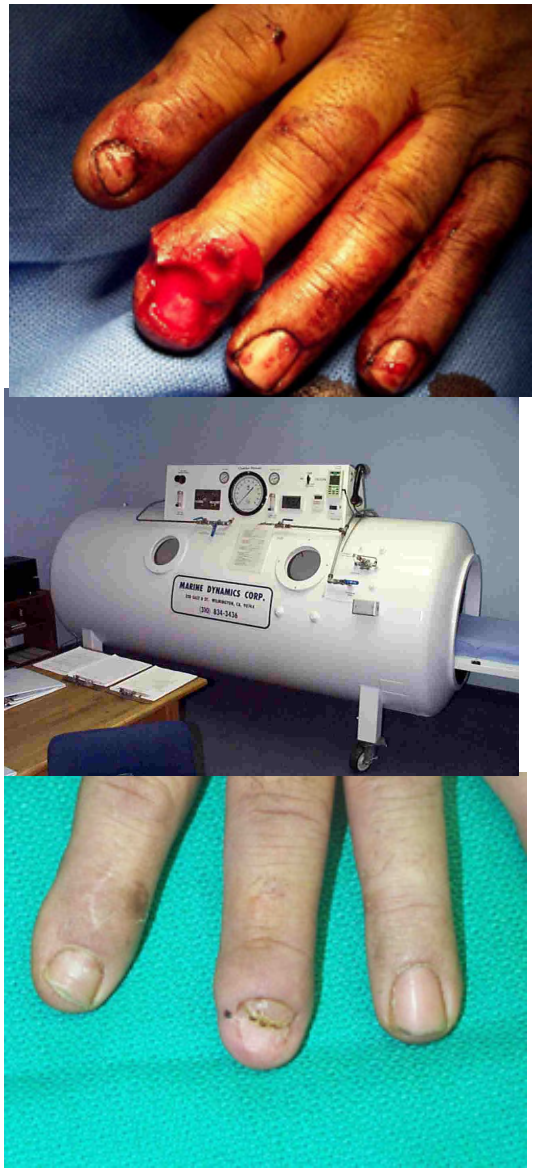
Good knowledge of armamentarium of antifungals


ECMM
CEMM


EFISG
ESCMID FUNGAL INFECTION
STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

Hyperbaric Oxygen Therapy

	N° 28
Mean age	31 (0.5-74)
Underlying diseases •Diabetes •Trauma •Others	 17 5 6
Principal site: CNS	21
Post operative	23/25 (92%)
Median sesssion	22 (2-85)
Overall Survival	86%
Better outcome 24 sessions Vs. 6	p= 0.009
Cut-off 9 sessions	p=0.003



Chamilos & Kontojiannis Clin Microbiol Infect 2005

ECIL-6

Strength of Recommendations	
Grade	**ECIL-5**
A	**Good evidence to support a recommendation for use**
B	**Moderate evidence to support a recommendation for use**
C	**Poor evidence to support a recommendation for use**

EFISG -2014

Grade of Recommendation	Definition
Grade A	ESCMID (EFISG) and ECMM **strongly** support a recommendation for use
Grade B	ESCMID (EFISG) and ECMM **moderately** support a recommendation for use
Grade C	ESCMID (EFISG) and ECMM **marginally** support a recommendation for use
Grade D	ESCMID (EFISG) and ECMM support a recommendation **against** use

Level of Evidence	Definition
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

	ECIL 6	EFISG
Surgery	A II	A II_U
Control underlying conditions	A II	A II_U
Prophylaxis ❖Posaconazole ❖Other azoles ❖Surgical resection	n.i.	 C III D II A III
Timely treatment	n.i.	A II_U

Legend: n.i. = no indication; u= uncontrolled trials

	ECIL 6	EFISG
Front-line Treatment		
❖L-AmB	B II	*A II_U
❖ABLC	B II	B II_U
❖ABCD	C II	n.i.
❖d-AmB	C II	D I
❖Posaconazole	C III	B II_U
❖Combination	C III	C III
Salvage		
❖Posaconazole	B II	A II_U
❖L- AmB	n.i.	B II_U
❖ABLC	n.i.	B II_U
❖Combo lipid AmB + Caspo	B III	C III
❖Combo lipid + Posa	B III	B II_U

Legend: n.i. = no indication; u= uncontrolled trials ; * (5 mg/kg)

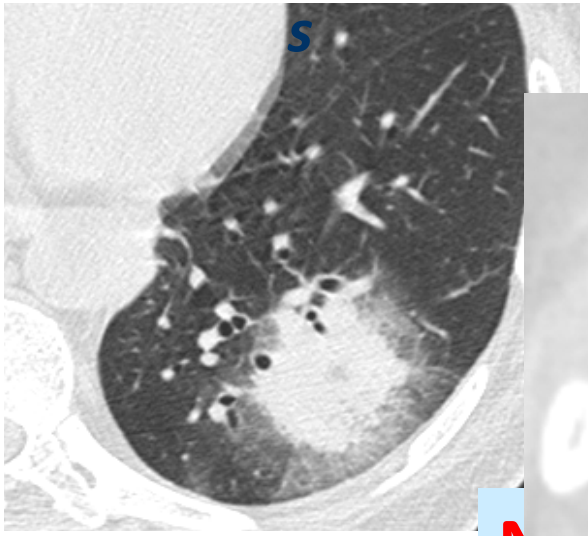
	ECIL 6	EFISG
G-CSF	n.i.	A II_U
Granulocyte transfusion	n.i.	C II_U
Hyperbaric oxygen	C III	C II_U
Maintenance ❖Posaconazole	B III	n.i.
Deferasirox ❖Hematological ❖No Hematological	A II (against)	D II C III

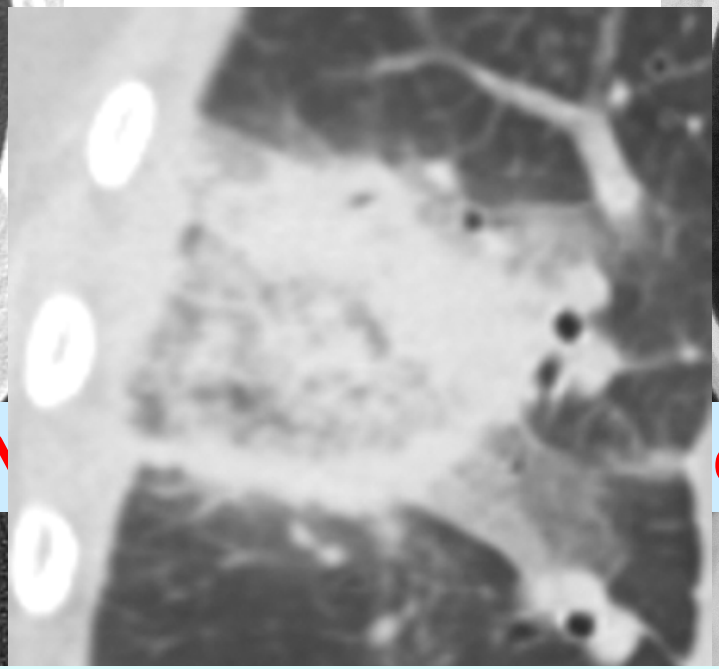
Legend: n.i. = no indication; u= uncontrolled trials

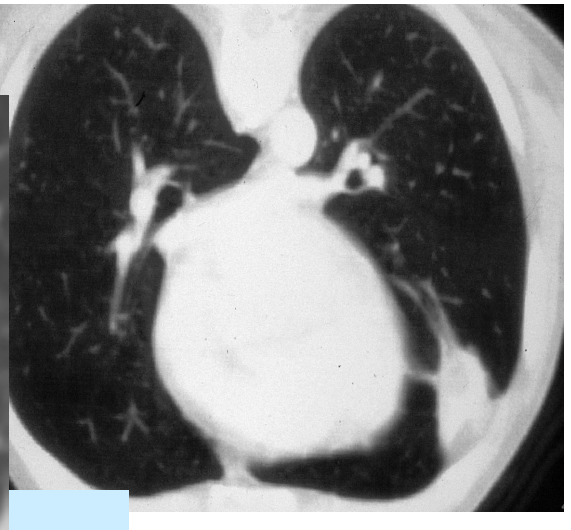
Radiological Pictures

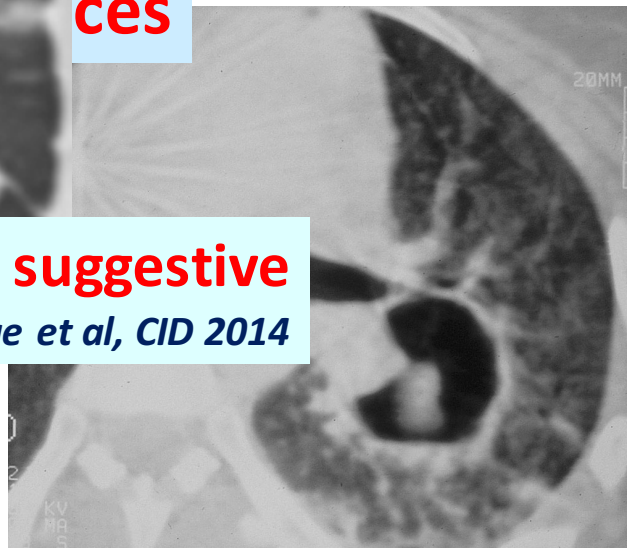
Mucormycete

Aspergillus





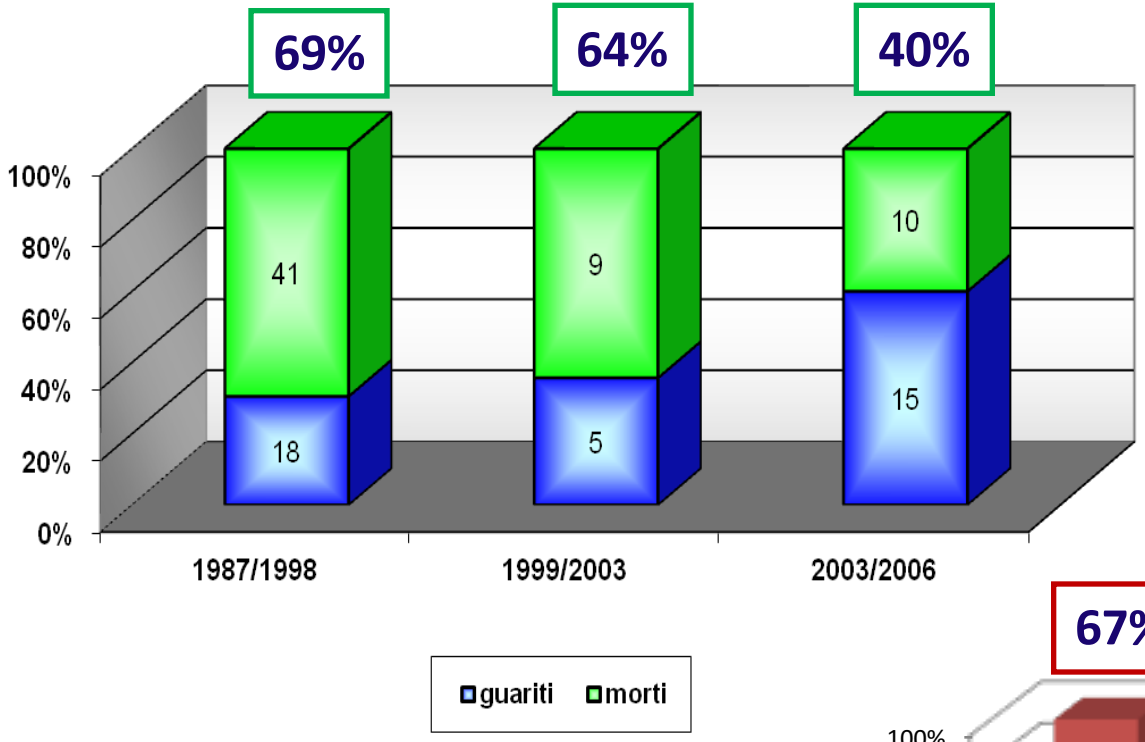




But "reversed halo sign" may be suggestive

Legouge et al, CID 2014

Mortality in HM patients



Italian experience

1987-2006

Pagano et al, J Chemother 2009

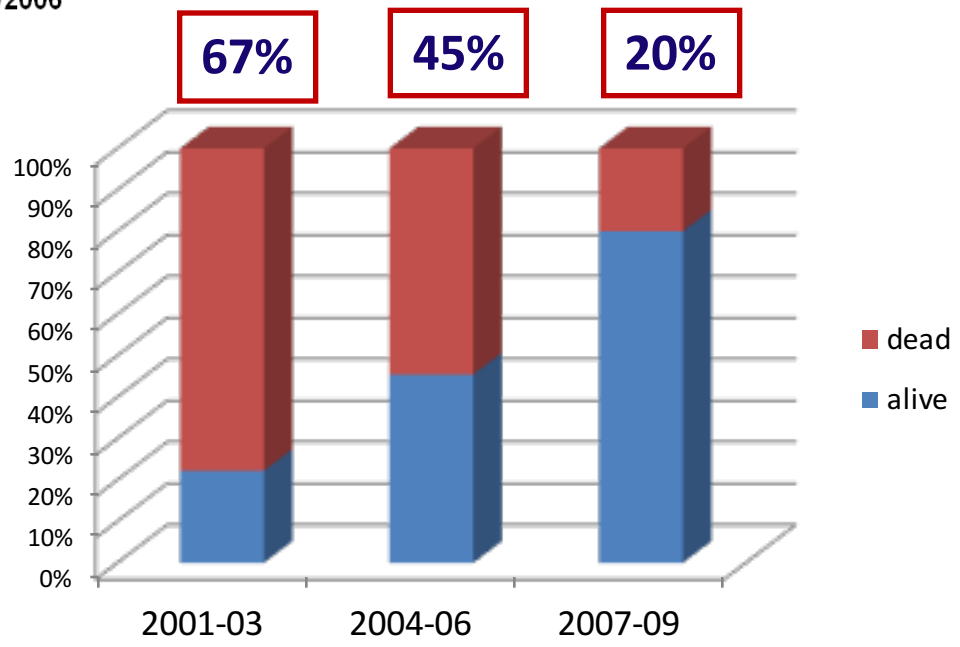
p-value 0.002

USA experience

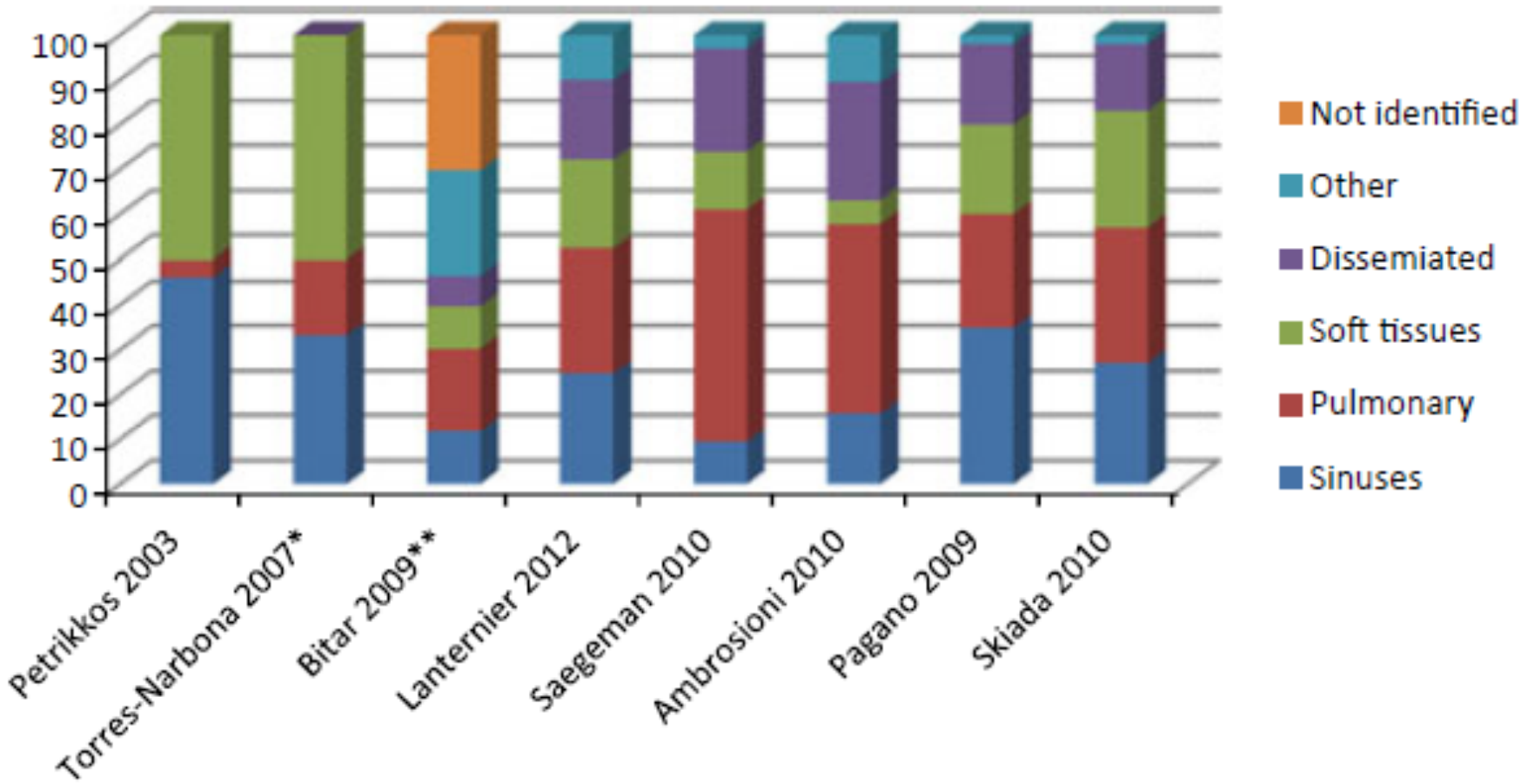
2001-2009

Hammond et al, Antimicrob Ag Chemother 2011

p-value 0.04



Distribution of clinical presentations



Petrikkos et al. CMI 2014

Mucormycosis in Organ and Stem Cell Transplant Recipients

Lanternier et al. Clin Infect Dis 2012

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 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%

Attributable mortality rate is near 70-75%

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2009, p. 3122–3125 Vol. 53, No. 7
0066-4804/09/$08.00+0 doi:10.1128/AAC.00361-09

Safety and Outcomes of Open-Label Deferasirox Iron Chelation Therapy for Mucormycosis[▽]

Brad Spellberg,[1,2]* David Andes,[3] Mario Perez,[4] Anne Anglim,[5] Hector Bonilla,[6] Glenn E. Mathisen,[7] Thomas J. Walsh,[8] and Ashraf S. Ibrahim[1,2]

patients treated with combination therapy including DFX at the dose of 15-20 mg/Kg

Risk factors	Site of infection	Antifungal agents	outcome
Diabetes SOT	Rhino-orbital-cerebral, lung, sinus, gastric	Lipid-AmB+ posaconazole Lipid-AmB+echinocandin monotherapy	5/8 cured

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

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

J Antimicrob Chemother
doi:10.1093/jac/dkr375

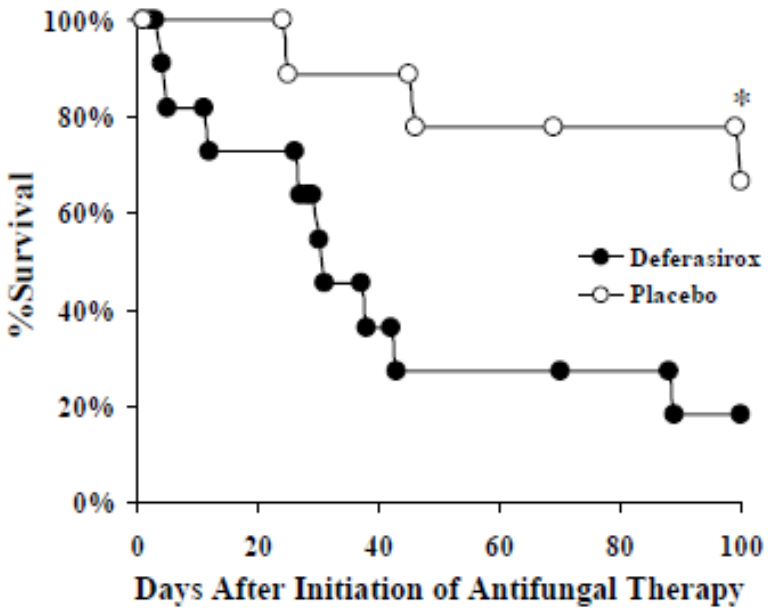


Figure 1. Time to death of patients randomized to deferasirox vs. placebo. All patients were followed through 90 days, with one death in the placebo arm captured on follow up of an SAE at day 100. *p = 0.04.

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

11 pts in L-AmB + deferasirox Vs. 9 L-AmB + placebo
Better results in diabetic patients

Diagnosis of fusariosis

★ Immunohistochemestry: **C III**

★ In situ hybridization: **C III**

Reagents not commercially available
Techniques not validated

Guarner & Brandt CMR 2011
Hayden Diagn Mol Pathol 2003
Montone AmJClinPathol 2009

★ β 1,3–D Glucan test & galactomannan: **B III**

Glucan usually positive, but not specific
Aspergillus GM sometimes positive in pts with fusariosis, GM may be useful for follow up

Tortorano et al, CMI 2014.

Diagnosis of fusariosis

★ Panfungal PCRs: **C II**

In house assays
In combination with conventional methods
High negative predictive value

Landlinger EJCMID 2009
Landlinger Leukemia 2010
Lau JCM 2007

★ Multiplex PCRs: **C III**

In house assays; not yet validated
Limited number of species covered

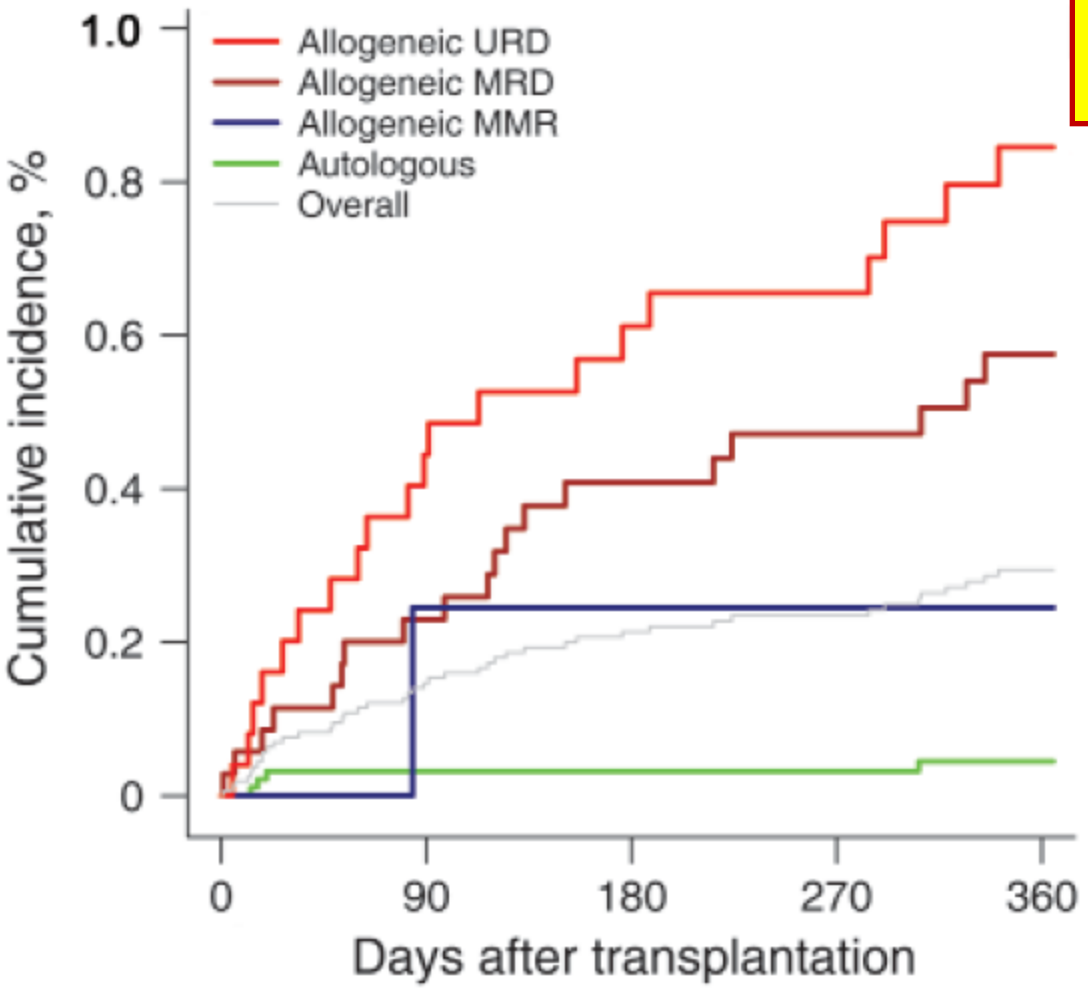
Lau JCM 2008
Spiess JCM 2007

Tortorano et al, CMI 2014.

Invasive Non-Aspergillus Mold Infections in HSCT Recipients, United States, 2001-2006

15,820 HSCT

77 with Mucorales/983 IFDs (0.08%)
Overall 12-month cumulative incidence: 0.3%



0.85%

Park et al, Emerg Infect Dis 2011

Adjunctive treatments for *Fusarium* infections

Hematological/neutropenic pts

★ Granulocyte transfusion +/- antifungals: **B III**

Boutati Blood 1997
Digani Leukemia 1999
Spielberger CID 1993
Helm JAAD 1990

Resolution of infection in pts who recovered of myelosuppression

Limited number of pts

Any patient population

★ Surgery: **A III**

To cure solitary lung nodules

Aggressive debridement of necrotic tissue

★ Catheter removal (+ antifungal): **A II**

To cure catheter related infection

Velasco EJCMID 1995

Treatment of *Scedosporium* infections

in immunocompromised pts

★ Voriconazole: **A II**

66% success rate (lowest in CNS or disseminated infection)

TDM required

Fortun EJCMID 2003
Heath CMI 2009
Husain CID 2005
Luijk Case RepInfDis 2011
Lamaris CID 2006
Klopfenstein MedPedOnc 2003

★ Liposomal AMB: **C III**

★ Conventional AMB: **D III**

Scedosporium spp usually resistant to AMB

High dosage required

Heath CMI 2009
Husain CID 2005

★ Combined therapy (Vori+LAmB; Vori+Caspo): **C III**

Unclear results

Case reports

Treatment of *Scedosporium* infections

★ GM-CSF combined with antifungals

in HSCT recipients: **B III** — Antachopoulos Immunother 2012

in CGD patients : **A II** — Bouza CID 1996; RodriguezTudela MM 2009

★ Surgical debridement

of infected bone/soft tissue: **B III** — Case reports

of pulmonary lesions in HSCT/SOT recipients: **C III** — Husain CID 2005

Laboratory diagnosis of *Scedosporium* infections

★ Culture: **A III** Growth in 3-4 days

- Immunocompromised pts:
  isolation from respiratory tract, sinuses, soft tissues, blood (mainly *S. prolificans*)

Cortez CMR 2008

- Near-drowning victims:
  isolation from aspiration or surgical drainage of brain abscesses (rarely from respiratory tract or csf)

- Cystic fibrosis pts:
  repeated isolation from respiratory tract as indicator of colonization

  selective media supplemented with cycloheximide or benomyl to allow growth of *Scedosporium* over other filamentous fungi

  disseminated infection in immunosuppressed pts (lung/liver transplant)

Borman MM 2010
Horrè Mycoses 2010
Cimon EJCMID 2000
Summerbell JCM 1993
Rainer AVanLeeu 2008

TABLE 4. Summary of recommendations for diagnosis of *Fusarium* infection

Fusarium infection/ Population	Test	SoR	QoE	Comment
Any population	Direct microscopy	A	III	Essential investigation
	Culture (species identification)	A	III	Essential investigation Easily recovered on routine mycological media without cycloheximide Accurate species assignment is important for guiding clinical management
	Histopathology	A	IIu	Essential investigation Features of hyaline septate hyphae (with acute angle branching) are similar to those seen with aspergillosis
	Immunohistochemistry	C	III	Not yet evaluated
	β-D-Glucan test/ Galactomannan	B	III	Glucan usually positive in case of invasive fusariosis. *Aspergillus* galactomannan sometimes positive in patients with fusariosis
	Pan-fungal PCRs for identification[a]	C	II	In combination with conventional methods High negative predictive values
	Multiplex PCRs[a]	C	III	Not yet validated Cover limited number of species/genera
	In situ hybridization	C	III	Not yet evaluated In-house tests
	Susceptibility testing	C	III	Gives an overview of drug activity and may be helpful in selecting antifungals
	Environmental sampling (and fungal typing)	A	III	In case of an outbreak situation
Haematological patients	Chest computed tomography (CT) scan	A	IIu	None of patients had normal CT Pulmonary nodules in 82% of patients

Tortorano et al, CMI 2014.

Identification of *Fusarium* species

★ Morphology: **A III**

Identification to genus or species complex level

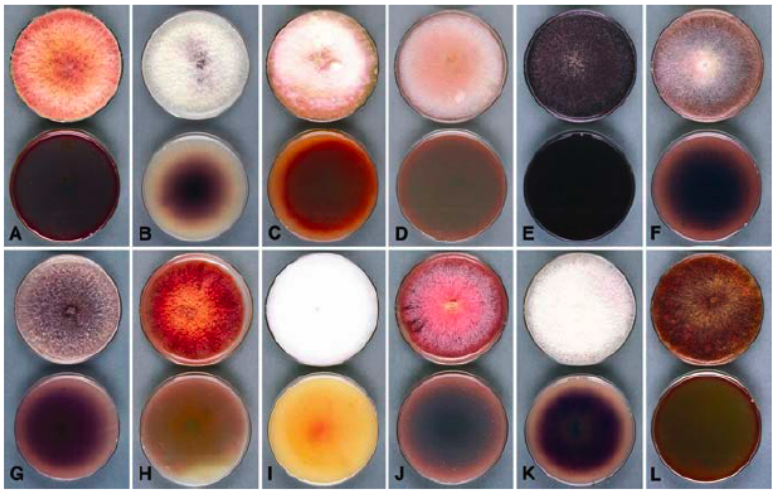


Fig. 2. Colony morphology of *Fusarium* species on potato dextrose agar. The top plate in each pair is the upper surface and the lower plate is the under surface. A, *F. poae*. B, *F. oxysporum*. C, *F. acuminatum*. D, *F. nelsonii*. E, *F. subglutinans*. F, *F. nygamai*. G, *F. pseudonygamai*. H, *F. lateritium*. I, *F. thapsinum*. J, *F. decemcellulare*. K, *F. verticillioides*. L, *F. culmorum*.

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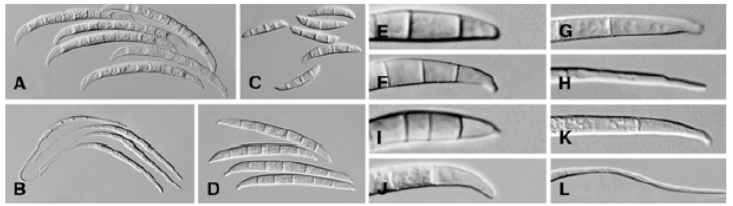

Fig. 6. Macroconidia of *Fusarium* species. A to D, Variation in macroconidial shape and length. A, *F. decemcellulare*. B, *F. longipes*. C, *F. culmorum*. D, *F. chlamydosporum*. E to H, Variation in basal cells of macroconidia. E, *F. culmorum*. F, *F. crookwellense*. G, *F. avenaceum*. H, *F. longipes*. I to L, Variation in apical cells of macroconidia. I, *F. culmorum*. J, *F. decemcellulare*. K, *F. verticillioides*. L, *F. longipes*.

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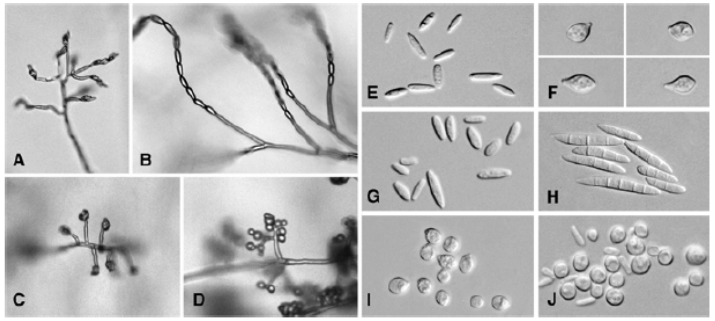

Fig. 4. Formation and types of microconidia produced by *Fusarium* species. A, Microconidia produced in short chains (*F. brevicatenulatum*). B, Microconidia produced in long chains (*F. decemcellulare*). C, Microconidia produced in false heads (*F. circinatum*). D, Napiform microconidia in false heads (*F. konzum*). E, Oval microconidia (*F. babinda*). F, Pyriform microconidia (*F. anthophilum*). G, Clavate microconidia (*F. anthophilum*). H, Fusiform microconidia (*F. semitectum*). I, Napiform microconidia (*F. poae*). J, Globose microconidia (*F. anthophilum*).

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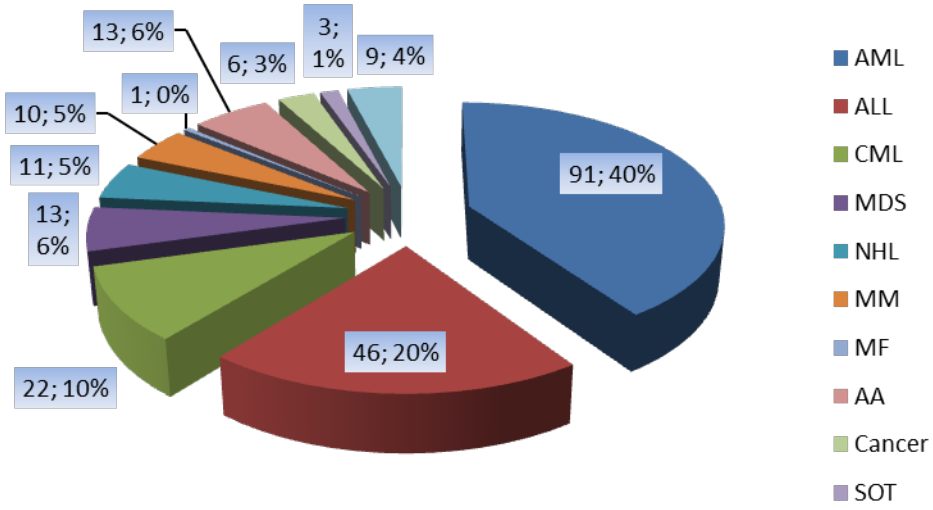
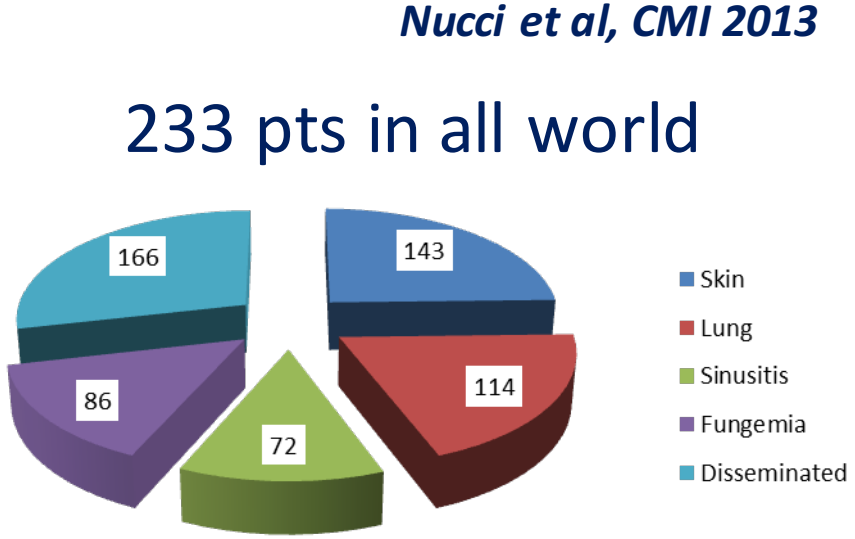
Improvement In The Outcome Of Invasive Fusariosis In The Last Decade

Nucci et al, CMI 2013





	Unadjusted		Adjusted	
	HR	P-value	HR	P-value
Hematological disease	5.70 (0.79-41.2)	0.08	5.26 (0.71-38.73)	0.11
Steroids	2.21 (1.24-3.94)	0.007	2.11 (1.18-3-76)	0.01
Neutropenia at end of therapy	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