Invasive fungal infections in our hospitals today

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FONDATION imagine INSTITUT DES MALADIES GÉNÉTIQUES

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Institut Pasteur

Transparency declaration

- ✓ Consultant to Gilead Sciences and received research grants or speaker's fees from Gilead Sciences, Merck, Pfizer, Astellas and Schering-Plough.

CURRENT HOST CHARACTERISTICS AND IFI BURDEN

Major host changes in our hospitals:

Sepsis, USA 1979-2000

Martin NEJM 2003

Characteristic	1979–1984 (N=1,332,468)	1985–1989 (N=2,220,659)	1990–1994 (N=2,697,472)	1995–2000 (N=4,068,819)
Demographic characteristics				
Age — yr	57.4±28.9	59.3±22.9	60.8±16.2	60.8±13.7
Chronic obstructive pulmonary disease	5.7	7.3	9.3	12.1
Diabetes	12.2	14.5	16.9	18.7

Diabetes UK 1996-2005

Gonzalez, J Epidemiol Community Health 2009

Diabetes incidence /100,000 p-yrs	1996	2005
Overall	2.71	4.42
Type 1		unchanged
Type 2	2.60	4.31
Obese type 2 (%)	46	56

820,900 people
123,205 deaths
97 prospective studies
HR of infectious death in diabetic pts:
2.39 (1.95-2.93)

Cambridge; NEJM, March 2011

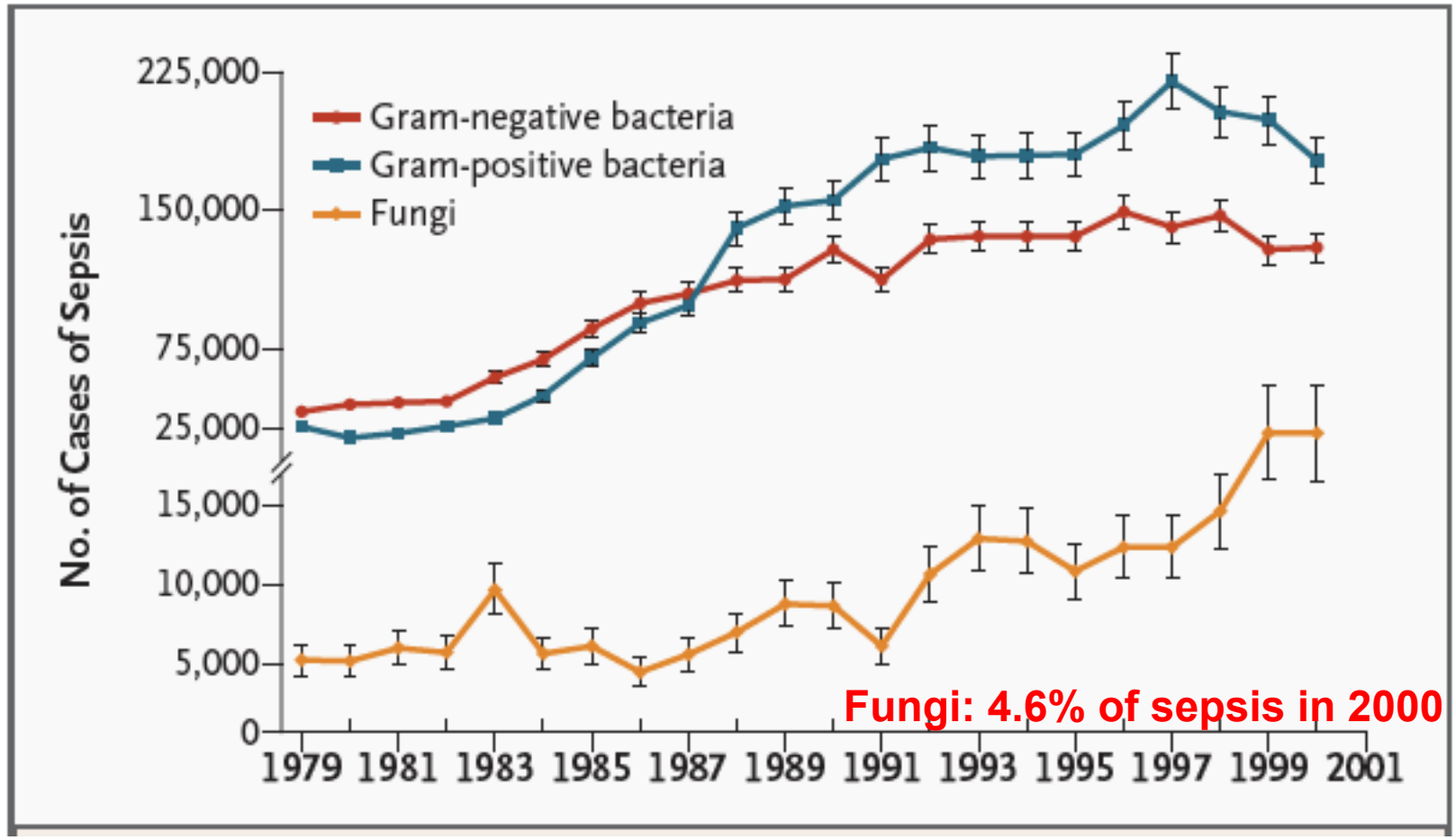
ICU patients: EPIC II study 2007

Characteristic	No. (%) All Patients (n = 13 796)[a]	Not Infected (n = 6709)[b]	Infected (n = 7087)[c]	*P* Value
Comorbid conditions				
COPD	2303 (16.7)	872 (13.0)	1431 (20.2)	<.001
Cancer	2086 (15.1)	975 (14.5)	1111 (15.7)	.06
Heart failure[f]	1342 (9.7)	604 (9.0)	738 (10.4)	.005
Diabetes mellitus	1336 (9.7)	605 (9.0)	731 (10.3)	.01
Chronic renal failure	1250 (9.1)	494 (7.4)	756 (10.7)	<.001
Immunosuppression	587 (4.3)	176 (2.6)	411 (5.8)	<.001
Cirrhosis	460 (3.3)	195 (2.9)	265 (3.7)	.006
Hematologic cancer	282 (2.0)	73 (1.1)	209 (2.9)	<.001
HIV	96 (0.7)	18 (0.3)	78 (1.1)	<.001
No. of comorbid conditions				
0	6686 (48.5)	3629 (54.1)	3060 (43.2)	<.001
1	4434 (32.1)	2076 (30.9)	2358 (33.3)	
2	1829 (13.3)	719 (10.7)	1110 (15.7)	
3	626 (4.5)	227 (3.4)	399 (5.6)	
>3	218 (1.6)	58 (0.9)	160 (2.3)	

51% pts infected: 19% fungi

Vincent JAMA 2009

207% increase in fungal sepsis : USA 1979-2000



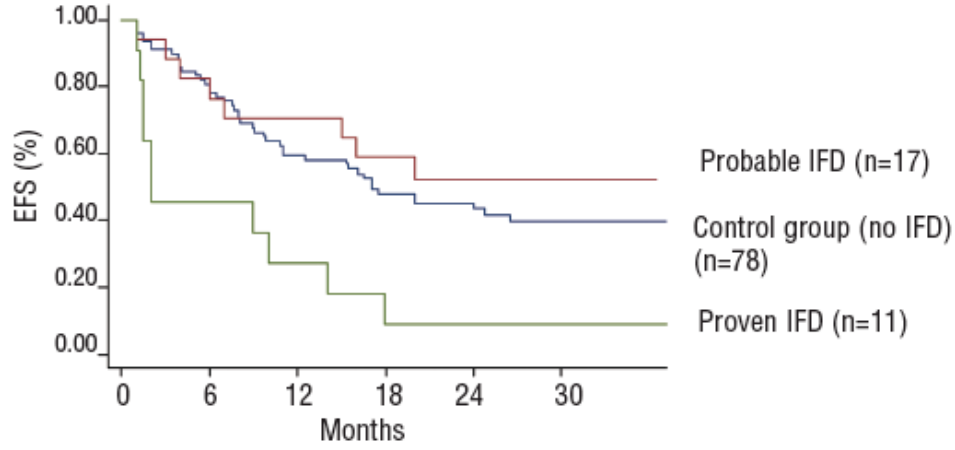
Martin, NEJM 2003

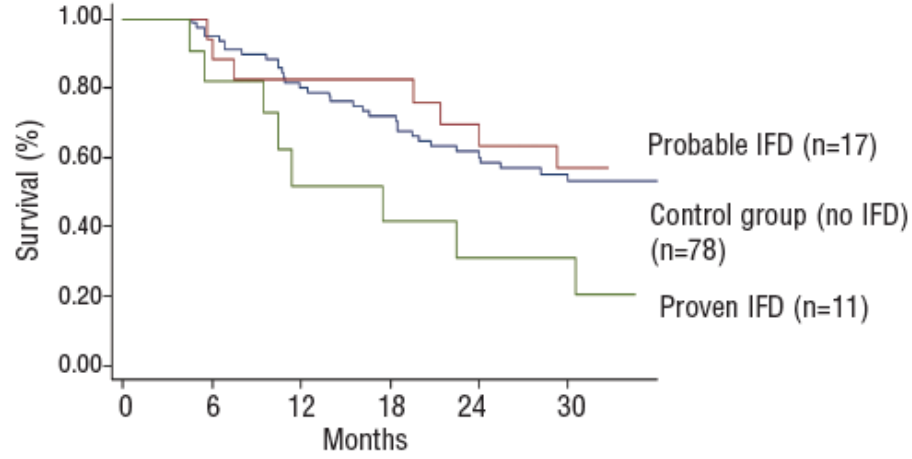
Current impact of candidemia in USA

Variable	Candidemia (n=8949)	Controls (n=17267)	Attributable increase (IC95%)
Mortality (%)	30.6	16.1	14.5 [12.1-16.9]
Length of stay (d)	18.6	8.5	10.1 [8.9-11.3]
Total cost ($)	66154	26823	39331 [3360-45602]

Zaoutis CID 2005.

Impact of proven IFI in acute leukemia patients





Even, Haematologica 2011

Current mortality rate of IFI in Europe

IFI	D 90 Mortality rate %	Reference
Candidemia (in ICU)	38 (46) [D 30]	Tortorano EJCMID 2004; Leroy CCM 2009
Aspergillosis (HSCT)	45 (56)	Lortholary, CMI April 2011 online
Cryptococcosis	23	Dromer, PLoS Med 2007
Mucormycosis (HM)	44-47 (60)	Lanternier, CID in press; Skiada, CMI 2011
Fusariosis	58	Lortholary, AAC 2010

Unchanged death rate during fungemia between 2002 and 2009 in Paris (2315 cases)
(Yeast Program, unpublished data)

IFI in our hospitals today: major players

Host

Classical hosts

Emerging risk factors

Abnormal immune restoration= IRIS

Fungi

Unmet Needs in Medical Mycology

Antifungal exposure

Three major : Aspergillus/Candida/PCP

Increasing role of zygomycosis

Nosocomial IFI

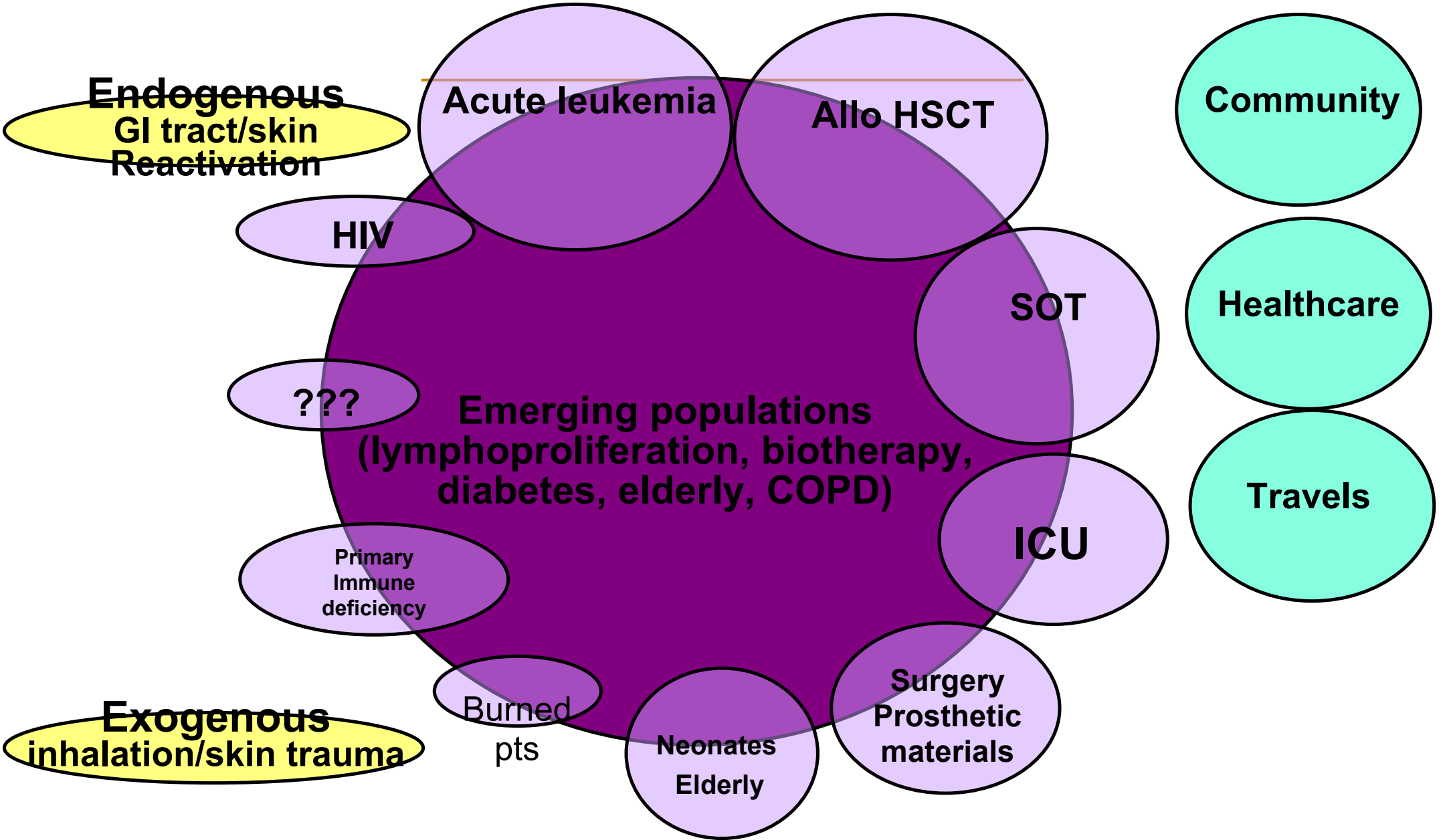
Emerging IFI/fungi

Fluconazole

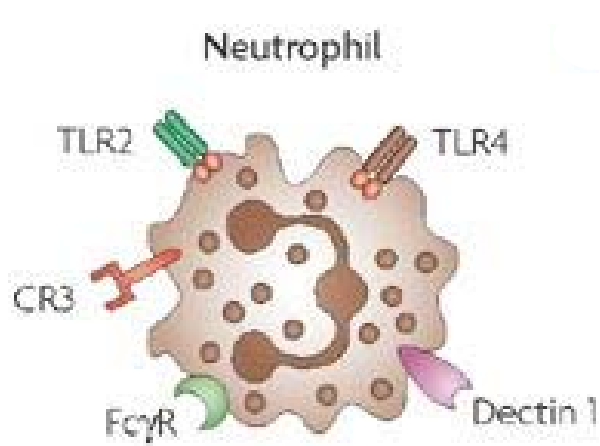
Voriconazole

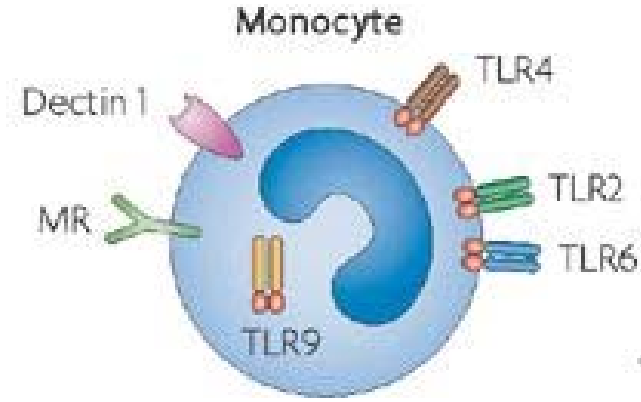
Echinocandins

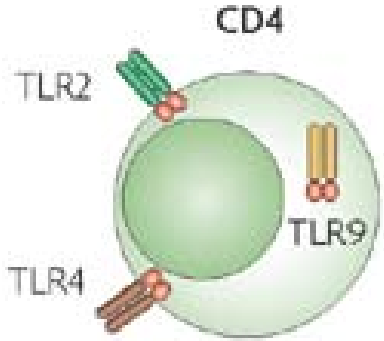
Risk factors for IFI



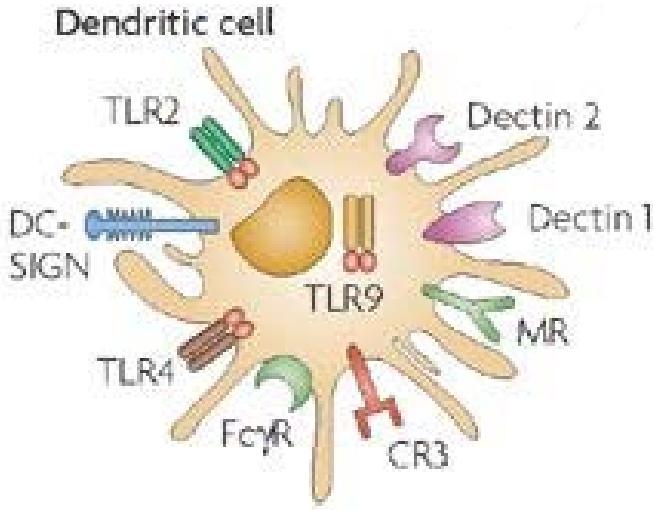
Key cells involved in the protection against fungi

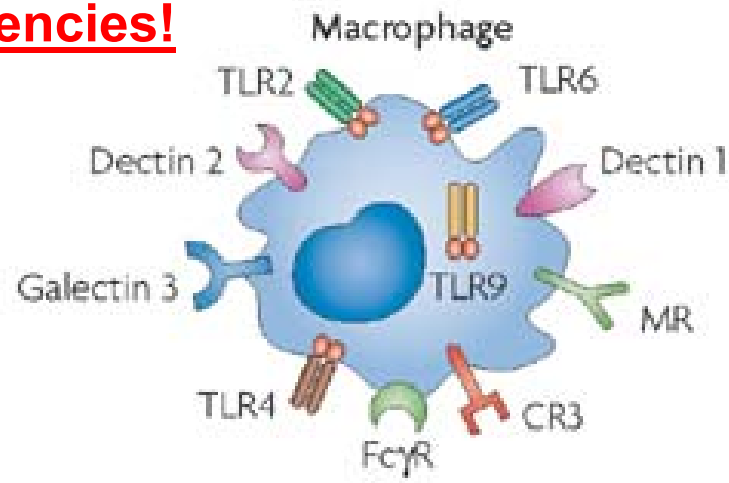






Combined deficiencies!





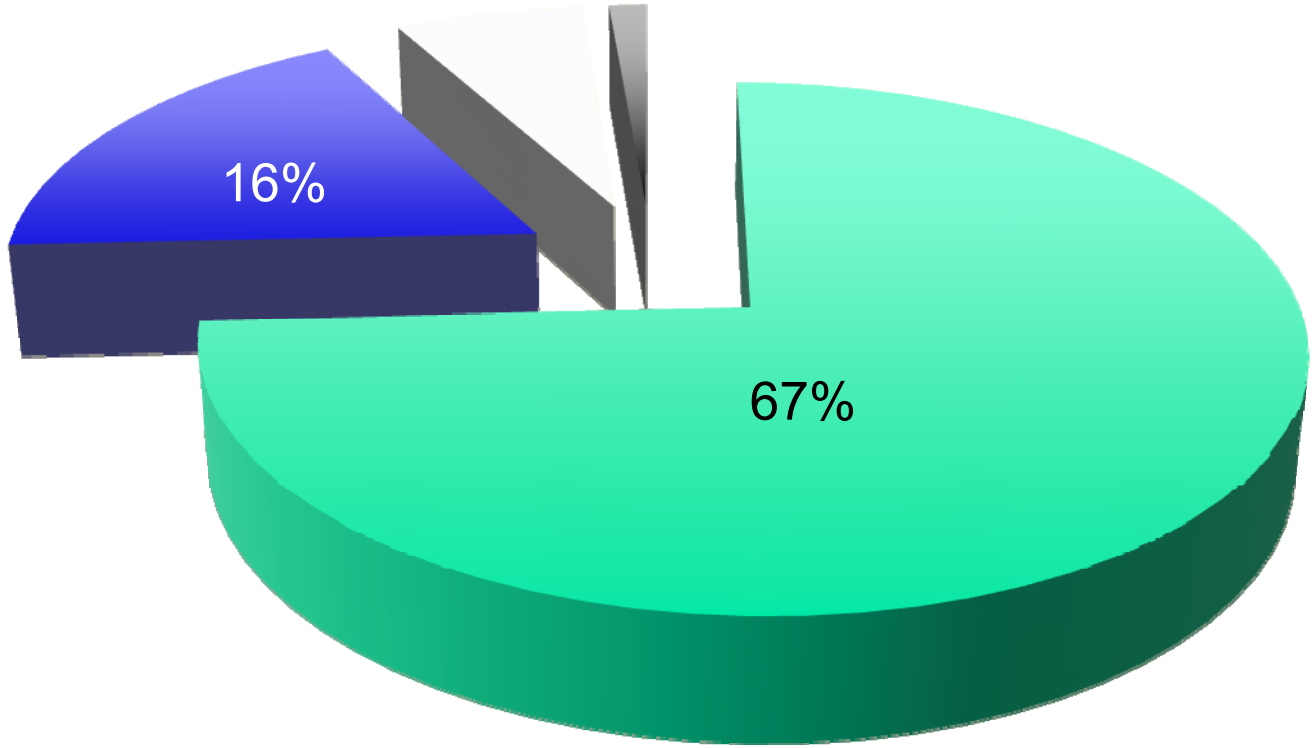
Netea Nature Rev Microbiol 2008

CLASSICAL HOSTS

- Acute leukemia
- HSCT recipients
- SOT
- HIV-infected patients still develop IFI
- Increasing role of ICU populations

Impact of acute leukemia on IA epidemiology

Non grafted acute leukemia = 34.4% of risk factors

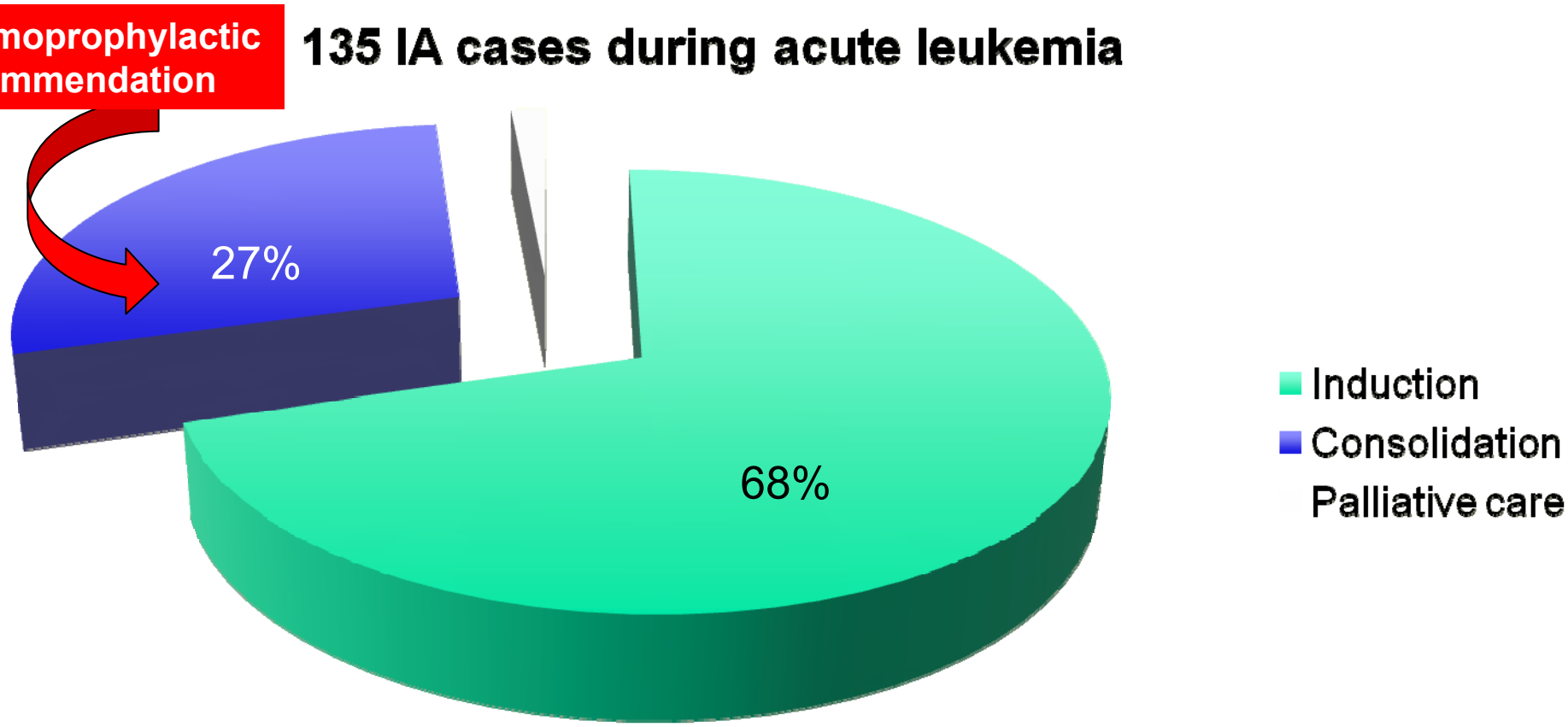


N= 393 adults

Lortholary, CMI April 2011 online

When does IA occur during acute leukemia?

No chemoprophylactic recommendation



Lortholary, CMI April 2011 online

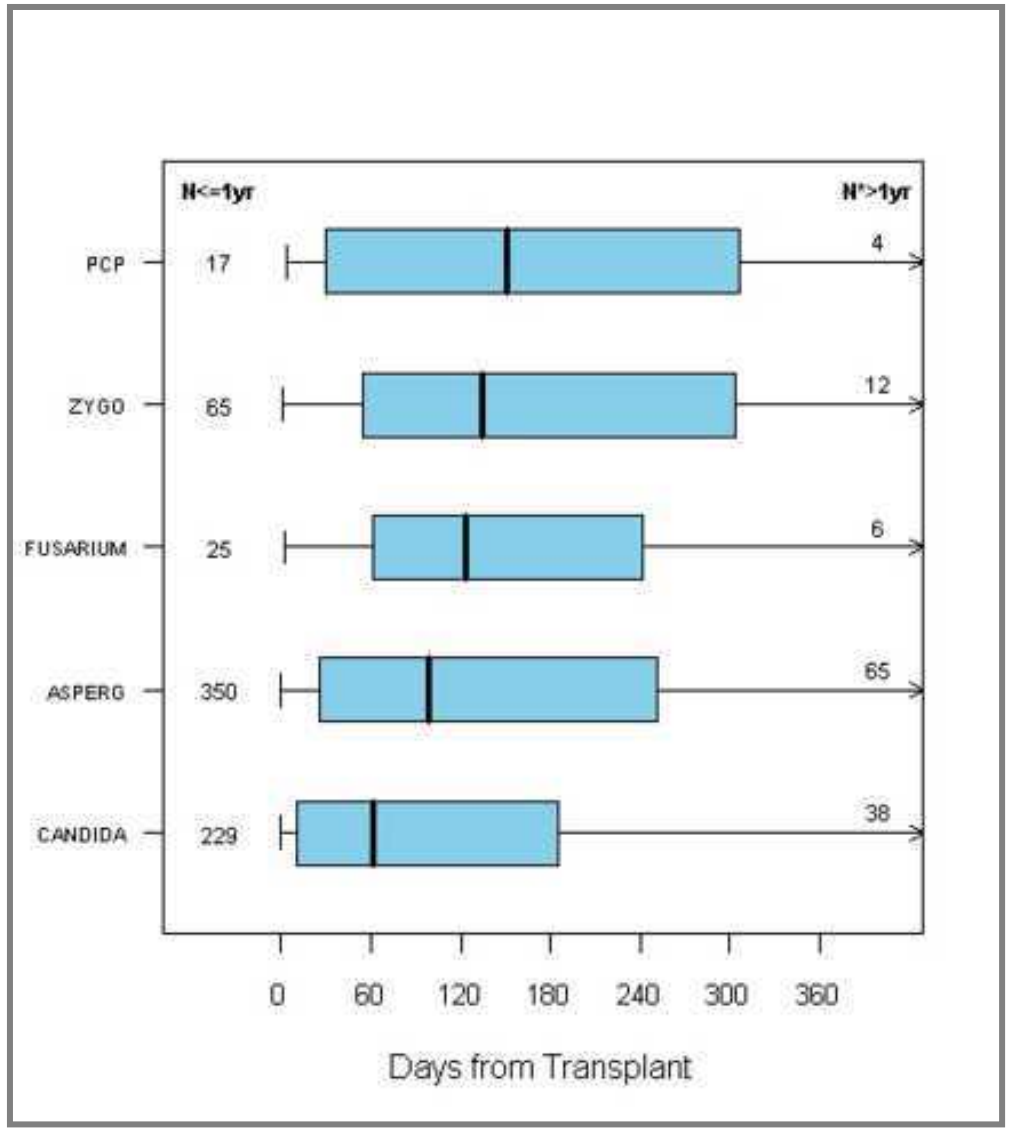
Candidemia in Hematology in Paris:
2315 cases, 2002-2009

	Hematological malignancy (n=409)	Non-hematology (n=1906)	p
Age	55±17	60±17	S
Prior FCZ	6.6%	5.1%	NS
Prior Caspo	6.4%	1.0%	S
C. albicans	45.2%	57.7%	S
C. glabrata	13.9%	18.1%	S
C. parapsilosis	11.5%	10.8%	NS
C. tropicalis	14.7%	7.8%	S
C. krusei	5.1%	2.1%	S
C. kefyr	4.4%	1.5%	S
Death (d30)	39.5%	41.2%	NS
% of death < d8	55.1	56.9	NS

Yeast Program, unpublished data

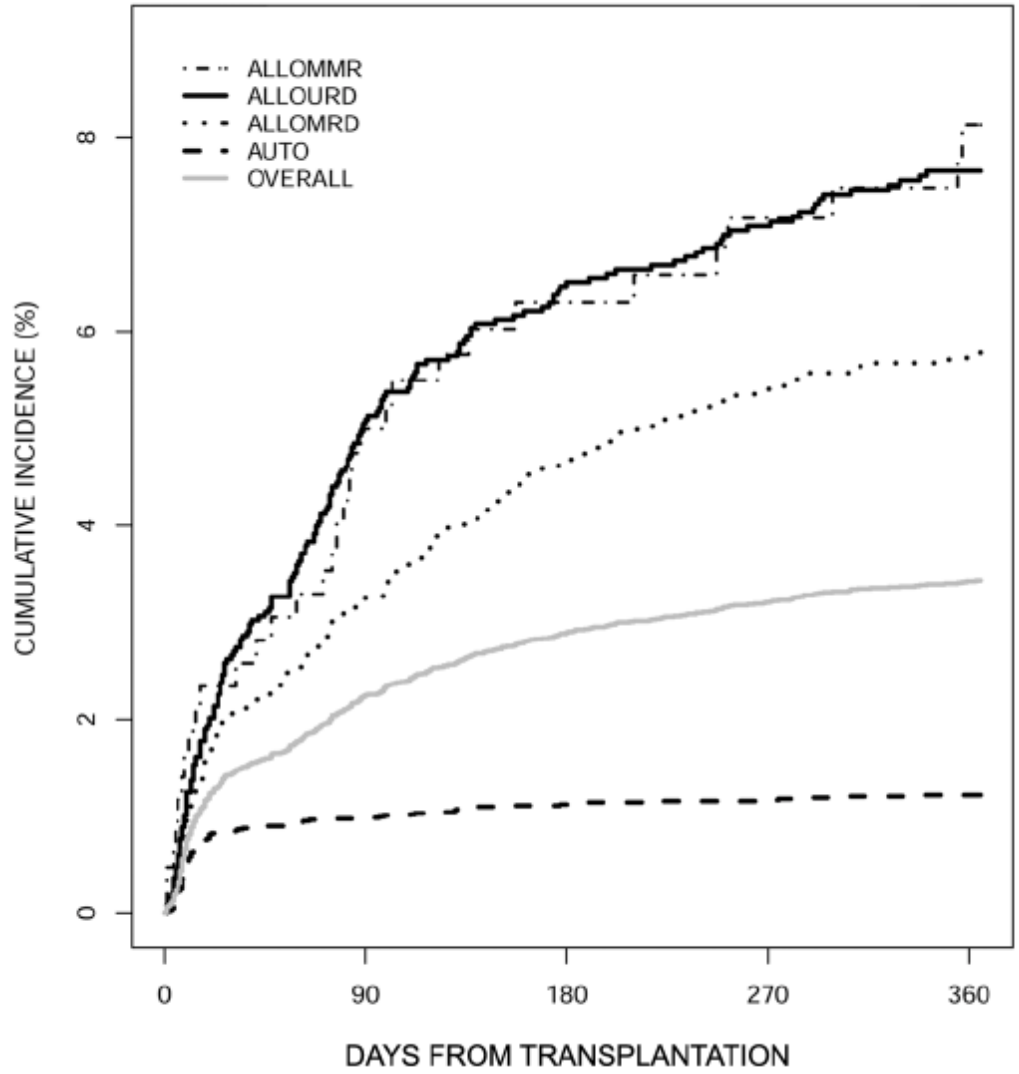
Median time to IFI in HSCT recipients:
TRANSNET data

23 US transplant centers
875 HSCT recipients



Kontoyiannis CID 2010

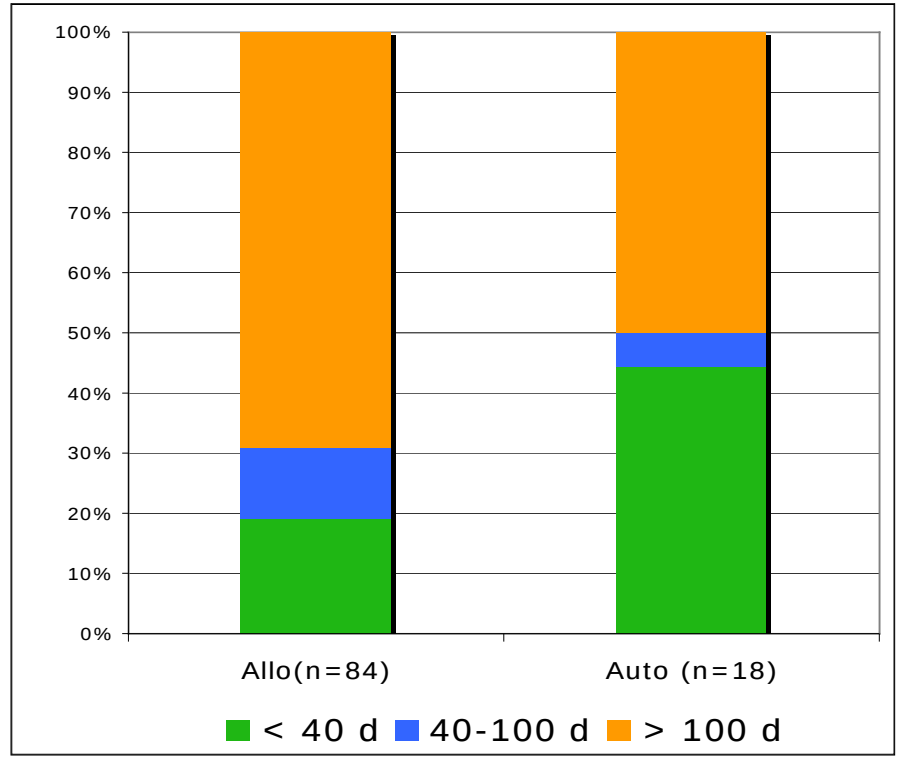
Cumulative incidence of IFI : stratification by type of HSCT



Kontoyiannis CID 2010

Incidence and time for invasive aspergillosis occurrence

- ✓ **Allogeneic HSCT**
  - **8.0%** [1]
  - **6.3%** [2]
  - **13.1%** [3]
- ✓ **Autologous HSCT**
  - **0.9%** [1]
  - **0.4%** [2]
- ✓ **Interval HSCT-IA**
  - **70% allo > 100 days** [4]
  - **50% auto > 100 days** [4]

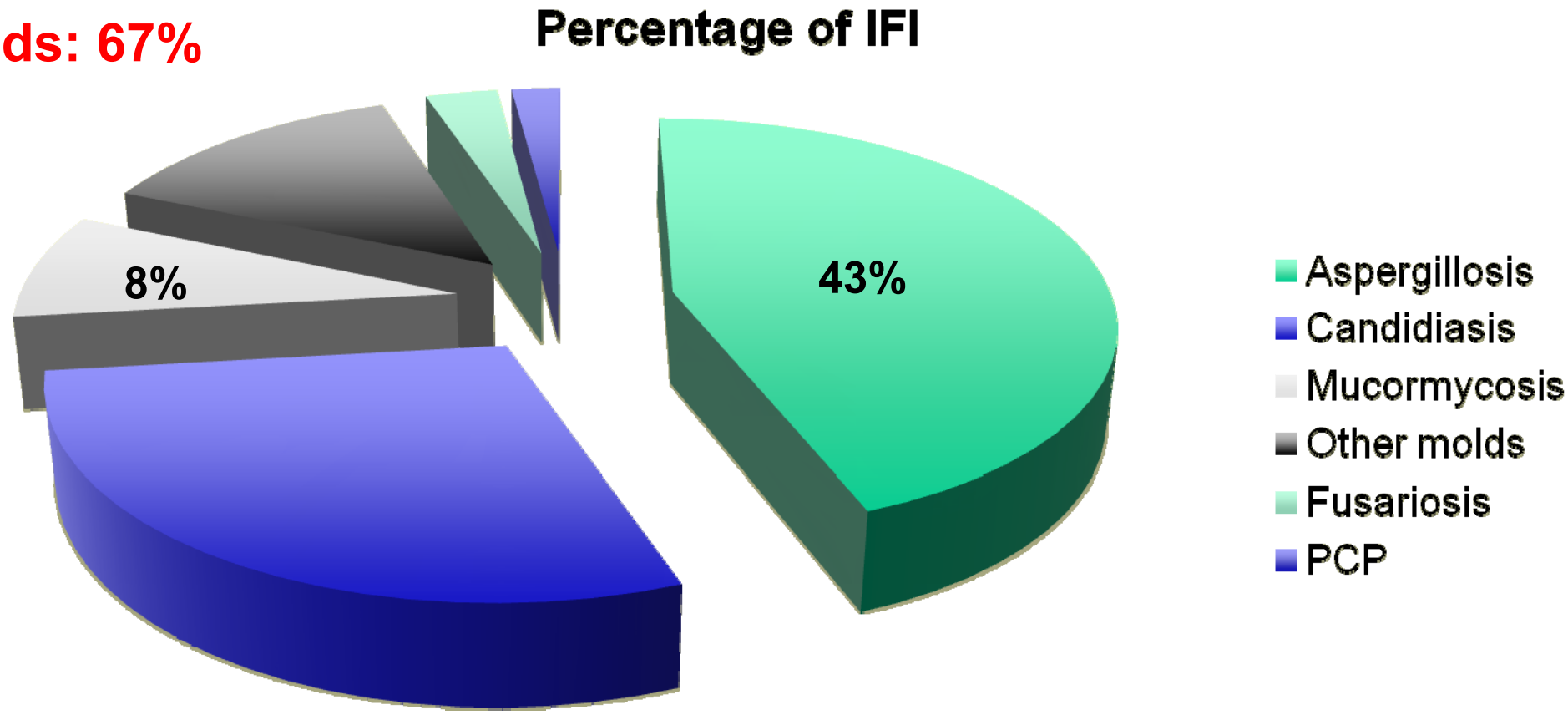


Lortholary, CMI April 2011 online

(1) Lortholary CMI April 2011 online; (2) Pagano, CID 2007; (3) Garcia-Vidal, CID 2008; (4) Neofytos, CID 2009

Distribution of IFI in HSCT recipients

Molds: 67%



Kontoyiannis CID 2010

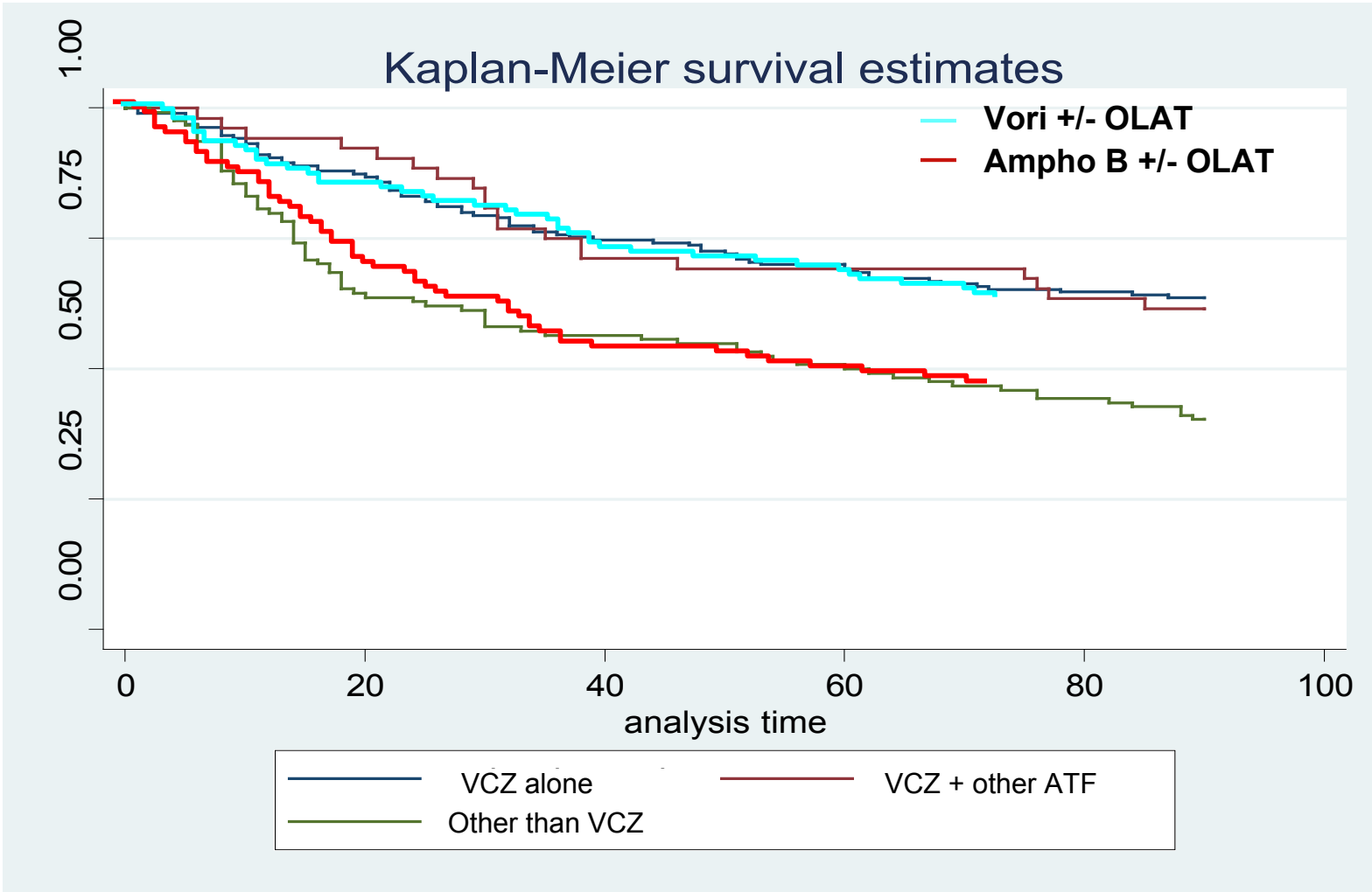
IA in HSCT recipients: potential viral co-infections

Patient, donor type	Reason for transplant	CMV status	Day BAL performed	Month of symptom onset	GVHD severity (onset, day after transplantation)	Copathogens	Day of death	Cause of death
1, unrelated	CML	D^-R^+	143	Jul 1999	None	PIV-3	166	Pneumonia (PIV-3)
2, unrelated	CML	D^+R^+	298	Mar 1999	Extensive (131)	CMV, RSV, *Staphylococcus aureus*	308	Pneumonia (polymicrobial)
3, unrelated	CLL	D^-R^+	11	Apr 1999	Extensive (150)	None (idiopathic pneumonia syndrome)		
			55			*Aspergillus niger* in BAL, *Aspergillus fumigatus* in sputum	154	Pneumonia (aspergillus, CMV)
4, matched-related	APML	D^-R^-	378	Apr 1999	None	RSV		
			409			*Aspergillus nidulans*	466	Pneumonia (aspergillus)
5, matched-related	AML	D^+R^+	159	Jan 1999	Extensive (150)	PIV-3, *Pseudomonas aeruginosa*	Alive	
6, unrelated	PCL	D^-R^+	4	Sep 1999	None	*Aspergillus* species	9	Pneumonia (aspergillus)

≥ 1 BAL + for HRV (PCR)

Ison CID 2003

Impact of initial therapy of IA



Herbrecht NEJM 2002.

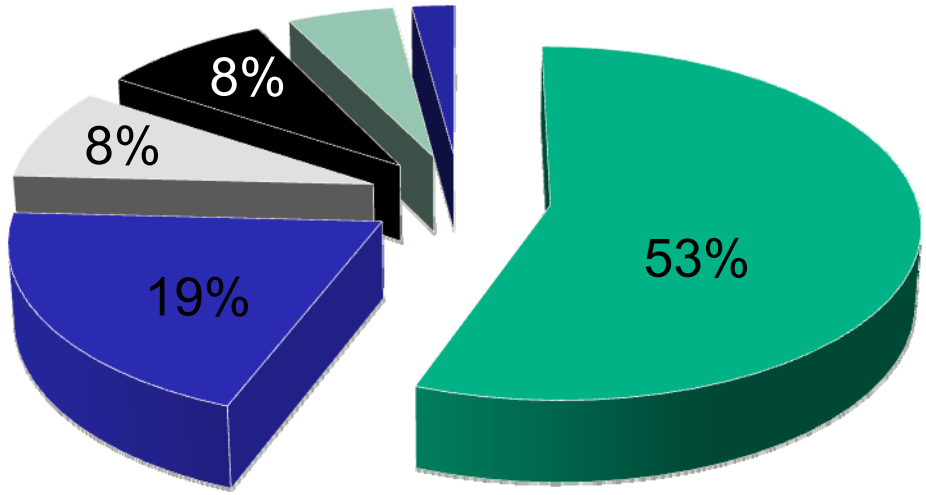
Lortholary CMI April 2011 online

« Breakthrough » IFI related to echinocandin therapy in Hematology

- **Failure due to susceptible isolates: *Aspergillus, Candida***
  - Walsh NEJM 2004, Lafaurie CMI 2010, Pfeiffer JCM 2010, Sun IJAA 2010
- **Failure due to emergence of intrinsically resistant/less susceptible species:**
  - Basidiomycetes (Sun IJAA, Suarez JCM 2010)
  - Mucorales (n=8) (Sujobert Open J Hematol 2010); *Fusarium* (Sun IJAA 2010)
  - *Candida parapsilosis* (Pfeiffer JCM 2010, Blanchard ECCMID 2011)
- **Failure due to acquired resistance in intrinsically susceptible Candida species:**
- Pfeiffer JCM 2010, Sun IJAA 2010, Dannaoui ECCMID 2010 (see infra)

Distribution of IFI in SOT recipients:
TRANSNET data

1208 IFI in 1063 organ transplant recipients



Median time post-transplant

- Candidiasis ⟷ 103 d
- Aspergillosis ⟷ 184 d
- Cryptococcosis ⟷ 575 d
- Non-Asp molds
- Endemic fungi
- Zygomycosis

Pappas, CID 2010

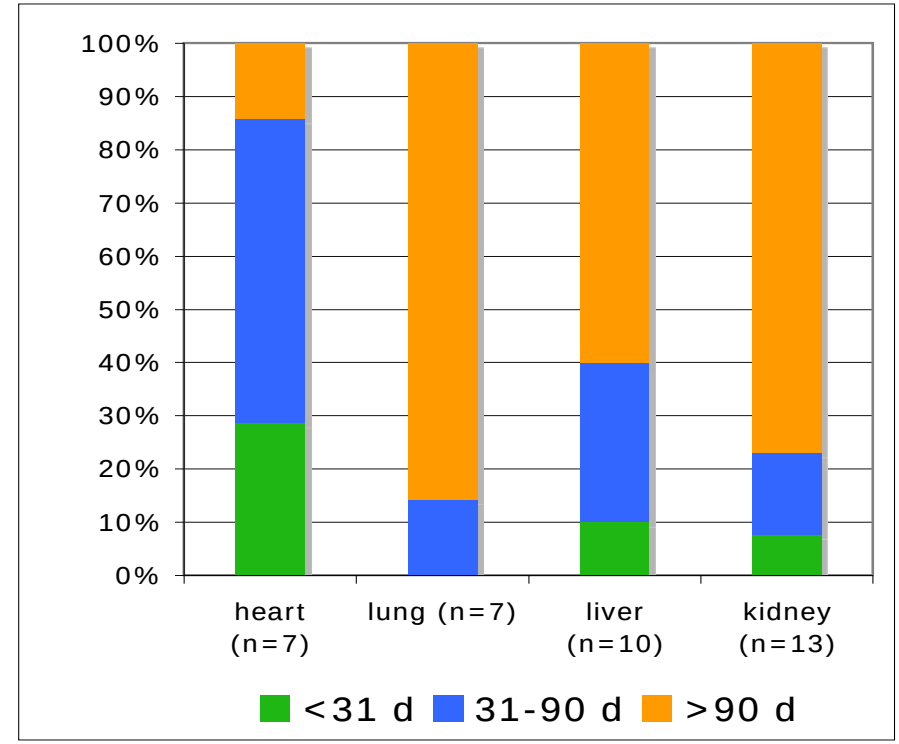
IFI by transplant type

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

Pappas, CID 2010

Incidence of IA in SOT recipients in France

- ✓ **Incidence**
  - **Heart 4.8 % (7/146) *(1)***
    - **1-14% *(2)***
  - **Lung 4.1 % (7/172) *(1)***
    - **6-16% *(2)***
  - **Liver 0.8 % (9/1067) *(1)***
    - **1-8 % *(2)***
  - **Kidney 0.3 % (13/3157) *(1)***
    - **0.4-5% *(2)***
- ✓ **Late complication excepted for heart transplantation**



(1) Lortholary, CMI April 2011 online; (2) Fernanda P et al, Medical Mycol 2007

Risk factors of IFI in SOT: aspergillosis and mucormycosis

- ✓ **Aspergillosis:** retrospective case-control study (OR)
- ✓ ≤ 3 months =
  - Difficult post-operative period (2.9)
  - CMV disease (2.3) & bacterial inf (3.2)
  - Renal failure (4.9)
- ✓ > 3 months =
  - Age > 50 yrs (2.5)
  - Isuppress related neoplasia (69.3)
  - Chronic rejection (5)
  - Renal failure (3.9)

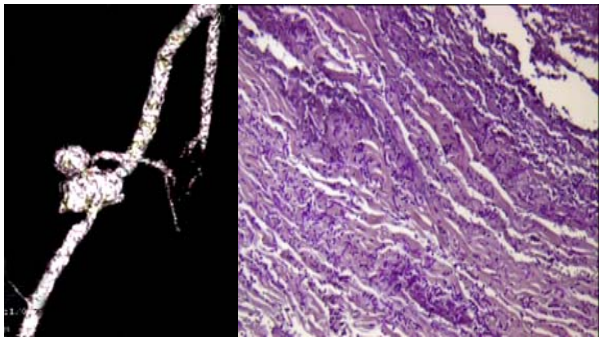
Gavalda CID 2005

- ✓ **Mucormycosis:** prospective international matched case-control study (OR)
- ✓ *higher risk* =
  - Renal failure (3.17)
  - Diabetes mellitus (8.11)
  - Prior voriconazole and/or caspofungin use (4.41)
- ✓ *lower risk* =
  - Tacrolimus (0.23)

Singh, JID 2009

Graft-transmitted IFI in SOT

✓ Candida (kidney)



1 per 1000
Same genotype
Preservation fluid
& graft site

✓ Crypto (USA)

Alleles

Locus	CAP59	GPD1	IGS1	LAC1	PLB1	SOD1	URA5
Allele Length	501	489	725	471	533	536	637
Patient 1 blood	8	10	15	8	12	3	11
Patient 2 blood	8	10	15	8	12	3	11
Patient 3 blood	8	10	15	8	12	3	11
Patient 3 CSF	8	10	15	8	12	3	11

✓ Endemic fungi

- Coccidioidomycosis
- Histoplasmosis

✓ Donor traveled in an endemic area

✓ Molds

- *Aspergillus*
- Mucorales

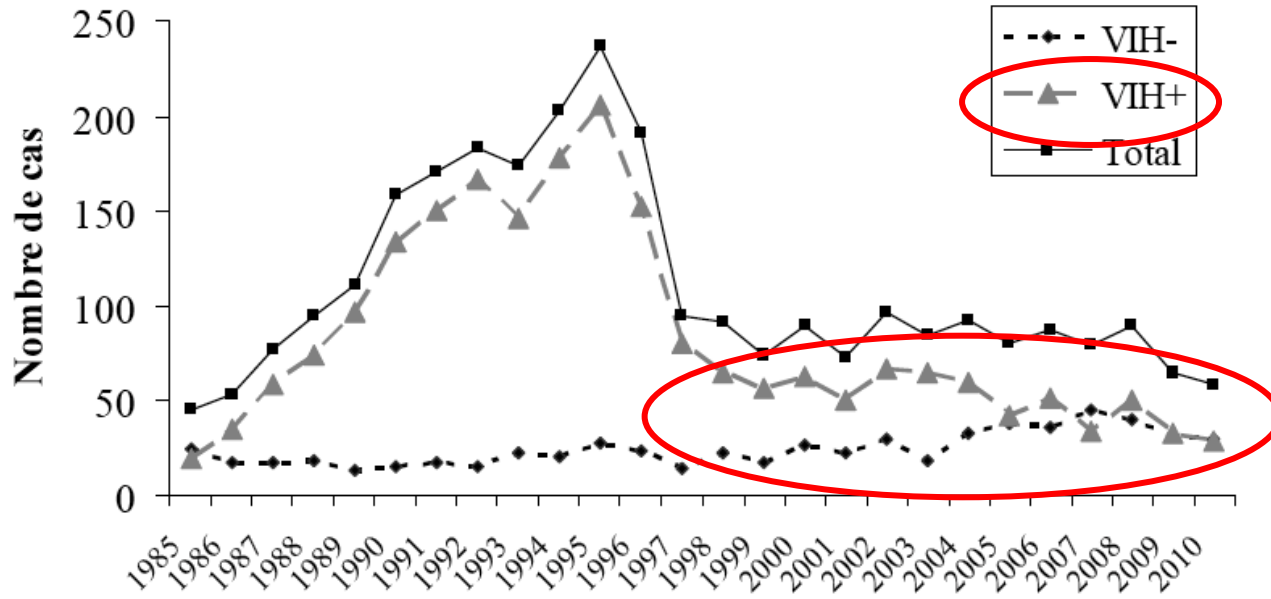
Albano, CID 2009; Baddley CID 2011; Botterel EJCMID 1999; Brugière Transplantation 2009; Keating Chest 1996; Rammaert CID in press

First AIDS-defining illness in France

Grabar HIV Medicine 2008

Fungal OI	1993-1995 (n=8027)		1998-2000 (n=3504)		2001-2003 (n=2396)	
	Rank	Rel Freq	Rank	Rel Freq	Rank	Rel Freq
PCP	1	15.6	1	19.9	2	19.1
Candida esophagitis	2	14.3	3	14.5	3	16.2
Crypto	14	2.2	12	2.7	9	2.9

Cryptococcosis in France Overtime (1985-2010)



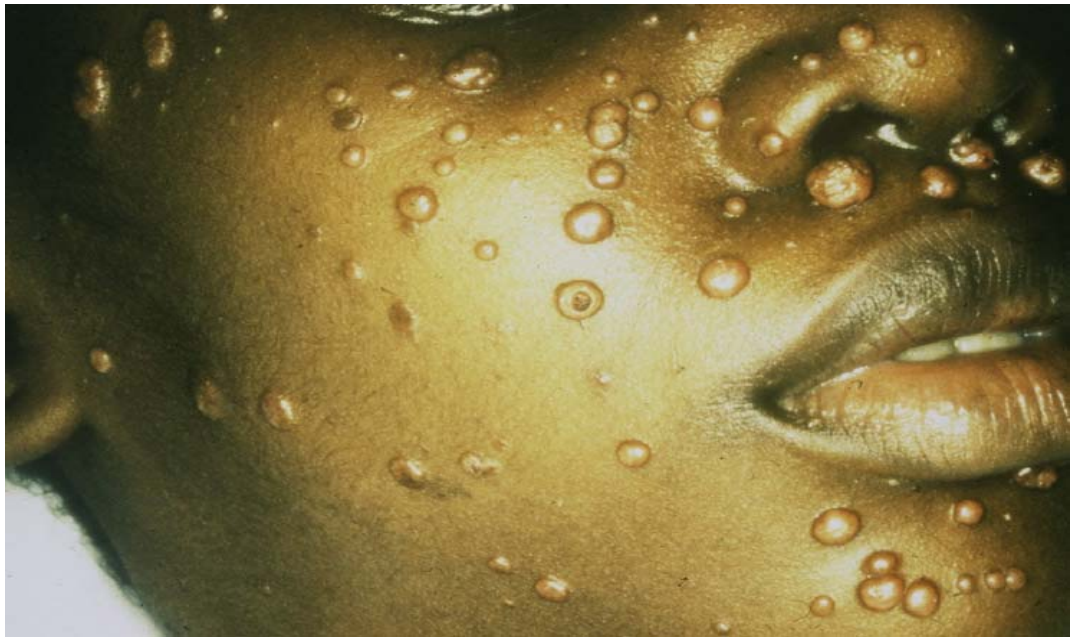
Imported var. *capsulatum* histoplasmosis in AIDS: France

Peigne, ECCMID 2011		Pre HAART (1985-1994)	HAART (1997-2006)	p
n		N = 43	N = 64	
Median age in years [95% CI]		39 (11)	40 (11)	0.62
Male, No. (%)		33 (77)	37 (58)	0.06
Continent of birth, No (%)				$< 10^{-3}$
	Africa	6 (15)	36 (58)	
	America	16 (40)	18 (29)	
	Europe	17 (43)	7 (11)	
	Asia	1 (2)	0	
	Oceania	0	1 (2)	
Mean CD4 cell count (/µl) (SD)		32 (6)	28 (7)	0.67
HIV status at the time of Hcc diagnosis, (No.%)				0.006
Histoplasmosis revealing HIV infection		7 (16)	27 (42)	

Southeast Asian HIV-infected patient in Paris…

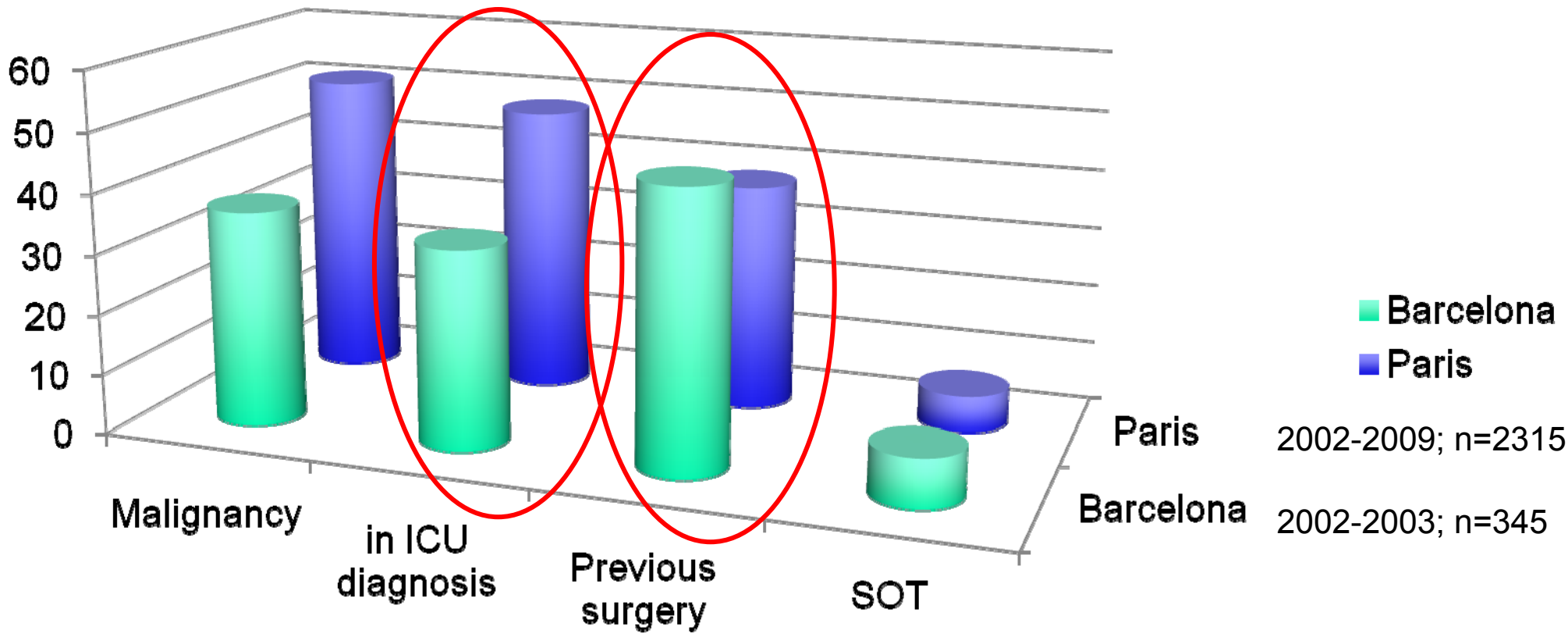
Penicillium marneffei

African HIV-infected patient in Paris…
Histoplasma caspsulatum var. *duboisii*



Loulergue, EID 2007

Candidemia in Europe today



Almirante, JCM 2005; Yeast Program, unpublished

Candidemia diagnosed in ICU in Paris: 2315 cases, 2002-2009

	ICU (n=1101)	Non-ICU (n=1214)	p
Age	59±17	60±17	NS
Prior FCZ	6.6%	4.2%	S
Prior Caspo	1.7%	2.1%	NS
C. albicans	54.7%	53.1%	NS
C. parapsilosis	8.8%	12.8%	S
Other species	-	-	NS
Death (d30)	50.5%	31.9%	S
% of death < d8	62.1	48.5	S

Yeast Program, unpublished data

Antifungal (mis)use in ICU

Azoulay, submitted

Fongiday®: 169 ICUs in France & Belgium; 2047 pts

154 pts (7.5 %) received ≥ 1 antifungal [100 without IFI]

60% fluconazole
24% caspofungin

INSTITUT ALBERT BONNIOT
ONTOGENESE ET ONCOGENESE MOLECULAIRES

Inserm
French Institute
of Health and Medical Research

SFAR

Société
de Réanimation
de Langue Française

In vitro susceptibility to fluconazole in ICU

- Prospective multicenter « Amarcand » study in France
- 305 identified isolates, 210 tested isolates
- **17 % R or S-DD to fluconazole** (validated methods)

Species	Distribution	*in vitro* susceptibility to fluconazole			DK
		Nb. tested	S	S-DD or R	
Candida albicans	174 (57%)	113	96%	4%	
Candida glabrata	51 (17%)	38	50%	50%	
Candida parapsilosis	23 (7,5%)	19	90%	10%	6%
Candida krusei	16 (5,2%)	6	17%	83%	
Candida tropicalis	15 (4,9%)	14	86%	14%	6.7%
Candida kefyr	11 (3,6%)	9	100%	0	
Candida guilliermondii	5 (1,6%)	5	80%	20%	
Candida lusitaniae	2 (0,7%)	2	100%	0	
Autres *Candida*	8 (2,6%)	4	50%	50%	
Total	305	210	83%	17%	

Leroy. Crit Care Med 2009; DK: Arendrup. JCM 2011

Candida peritonitis in ICU
Amarcand Study, 2005-2006

- **93 cases among 271 ICU pts with invasive candidiasis**
  - 73 nosocomial
  - 53 with concomitant bacterial peritonitis
  - 26 with candidemia

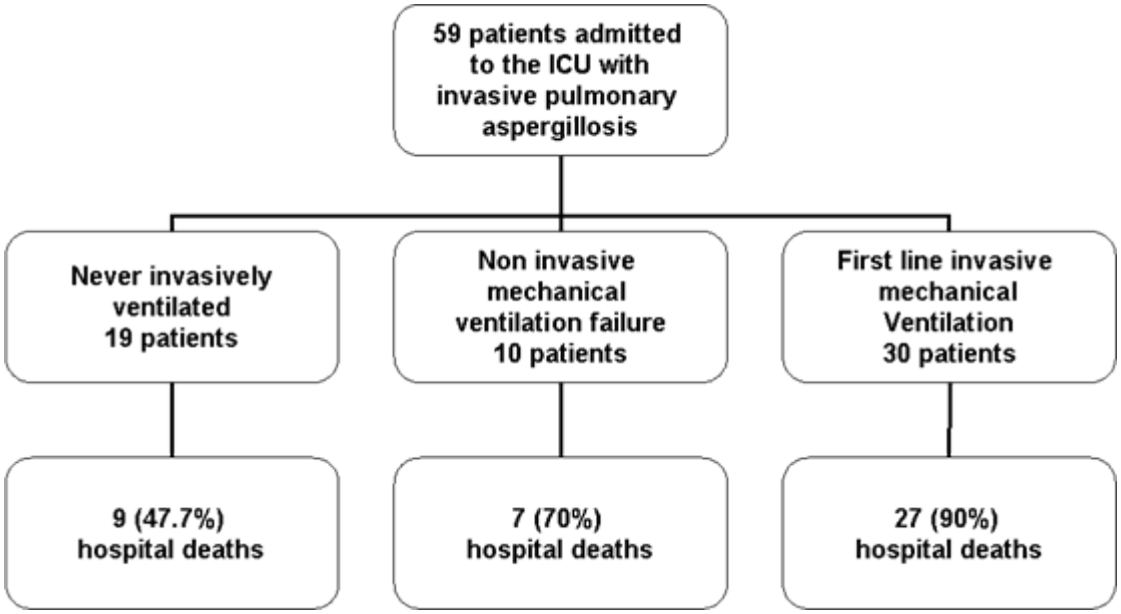
  - **58% *C. albicans***
  - **20% *C. glabrata***

  - **Overall 28% of episodes due to SDD or R FCZ isolates**

Montravers, CMI 2010

Invasive aspergillosis in our ICUs

Hematology patients



Burghi, St Louis Hosp, Paris, submitted

Non-hematology patients

- ✓ 2.3% of IA in France
- ✓ Role of steroids in COPD [≥ 0.7 mg/kg/d in 13/13 fatal cases]
- ✓ Admission in ICU predictive of IPA in case of *Aspergillus* isolation in COPD
- ✓ Low sensitivity and variable specificity of culture
- ✓ BAL GM (and no serum GM):
  - 88% sensitivity
  - 87% specificity
- ✓ ≥ 50% mortality

Lortholary, CMI in press; Ader CMI 2005; Guinea CMI 2010; Meersseman CID 2007, ARRDCCM 2008

IFI outbreaks: yeasts, PCP, molds

YEASTS

- ✓ 1/3 of candidemia = nosocomial clusters
- ✓ Cluster ≠ Clonal
  - *C. krusei* (Finland, Portugal)
- ✓ Clonal:
  - *C. parapsilosis*
    - Italy, Sweden
  - *C. albicans*: France
  - 5FC R *C. tropicalis*: France

Asmundsdottir CID 2008, Hautala BMCID 2007, Ricardo CMI 2011, Posteraro ICHE 2004, Brillowska-Dabrowska ScandJID 2009, Lasheras JHI 2007, Desnos-Ollivier EID 2008

PCP

- ✓ Inter-patient contacts
- ✓ Lack of isolation measures
- ✓ Typing: predominant or single strain

De Boer Med Mycol Apr 2011

MOLDS

***Aspergillus* spp.**	Building construction Ocular surgery Syringe for spinal anaesthesia Air handling-system Adhesive tape Outside packages of dressing supplies
***Fusarium* spp.**	Hospital water systems
Phialemonium curvatum	Syringes for intracavernous penile injections
Paecilomyces lilacinus	Skin lotion Neutralizing solution for intra-ocular lens implantation
Acremonium kiliense	Ventilation system of ophthalmologic operating room
Exophialia jeanselmei	Deionized water used to prepare antiseptic solutions
Scedosporium prolificans	Airborne contamination Renovation

Medical devices as a source of nosocomial mucormycosis (Rammaert, CID in press)


Chen F, Eur spine J 2006

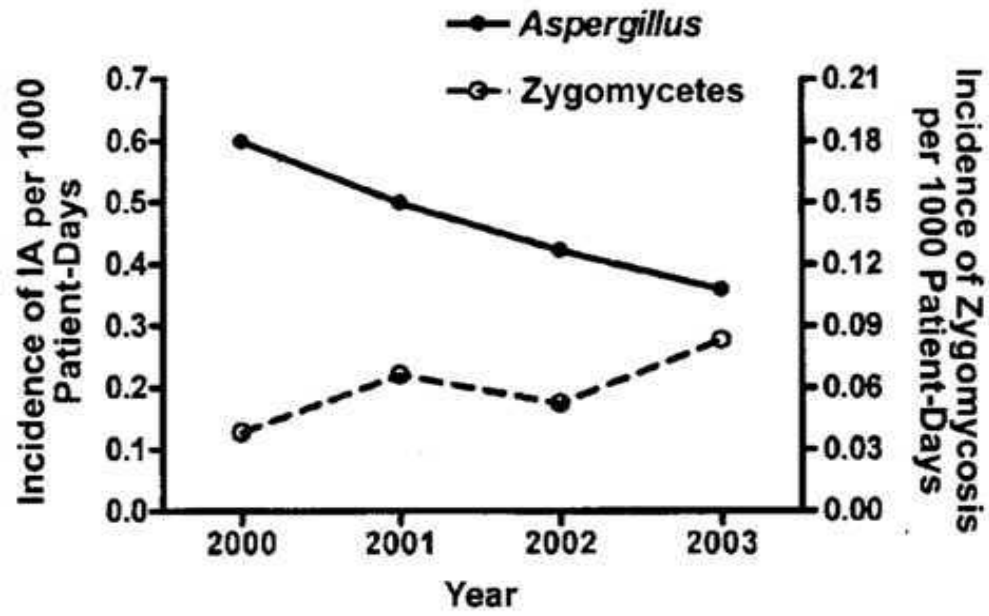
IMPACT OF EXPOSURE TO ANTIFUNGALS

- Voriconazole
- Fluconazole
- Echinocandins

Does voriconazole impact the occurrence of mucormycosis in hematology?

An observational, MD Anderson study (2002-2004)

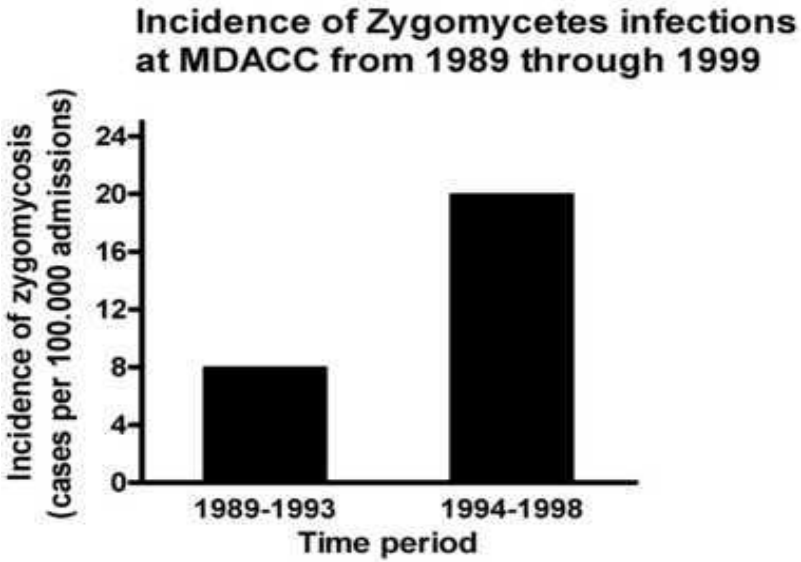
	Zygo (27) (%)	Asp (54) (%)	*P*
VRC Prophy. (≥5d)	48	11	.001

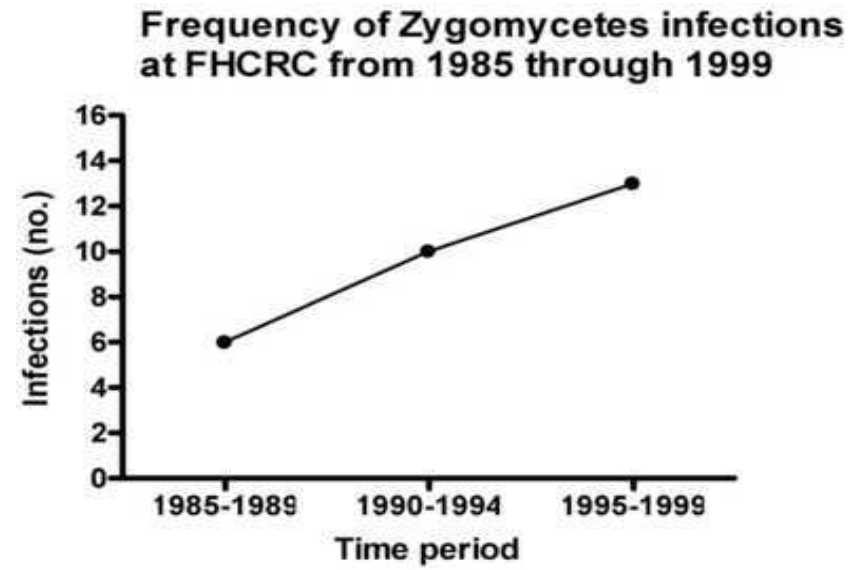


Apache II >16 at dx: 6/27 (22%)
ICU at dx: 10/27 (37%)

Kontoyiannis J Infect Dis 2005

But… emergence of mucormycosis has preceded VRC use in US cancer centers





Kontoyiannis et al. CID 2000

Marr et al. CID 2002

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

Emerg Infect Dis Sept 09

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

National Hospital Database

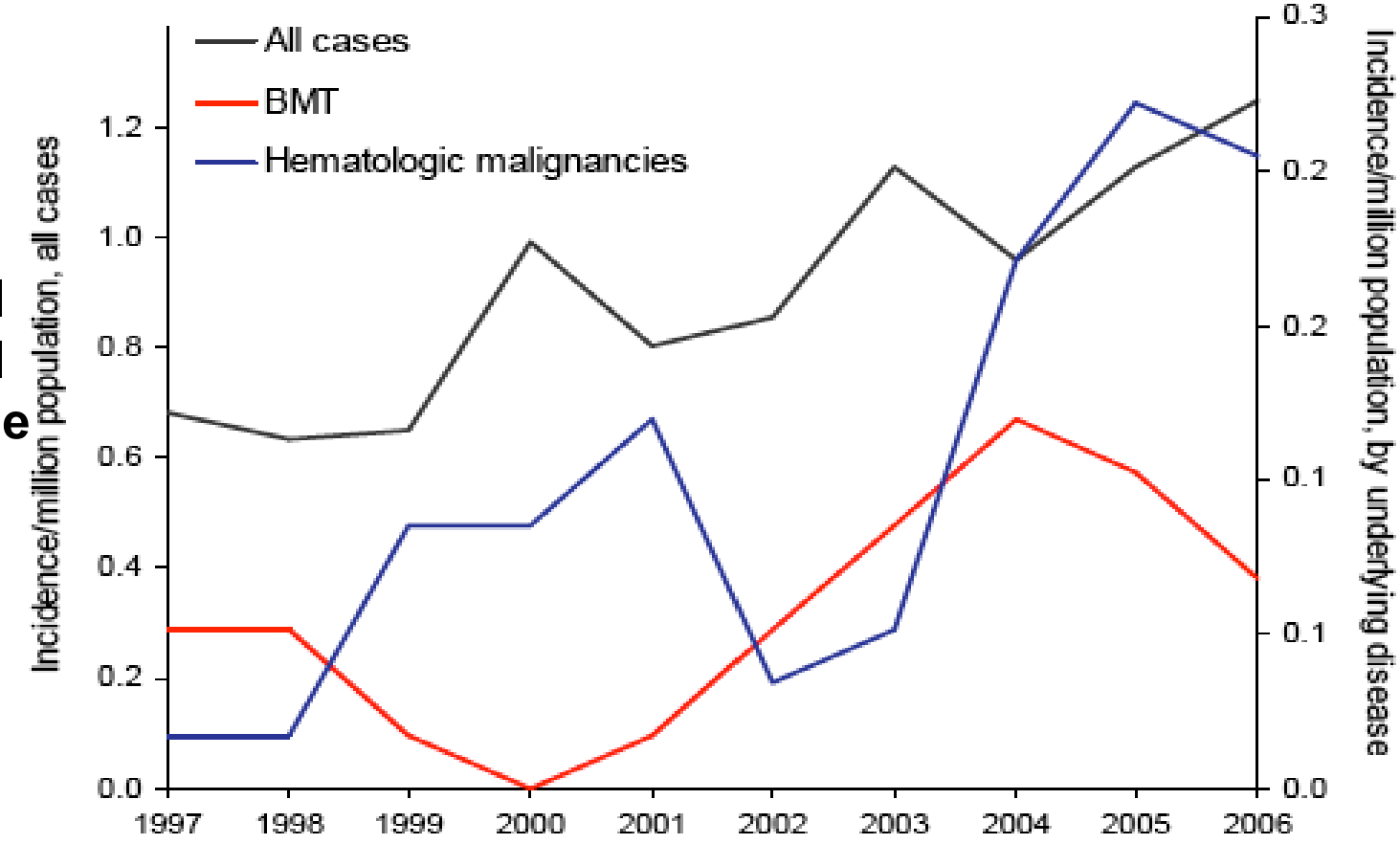
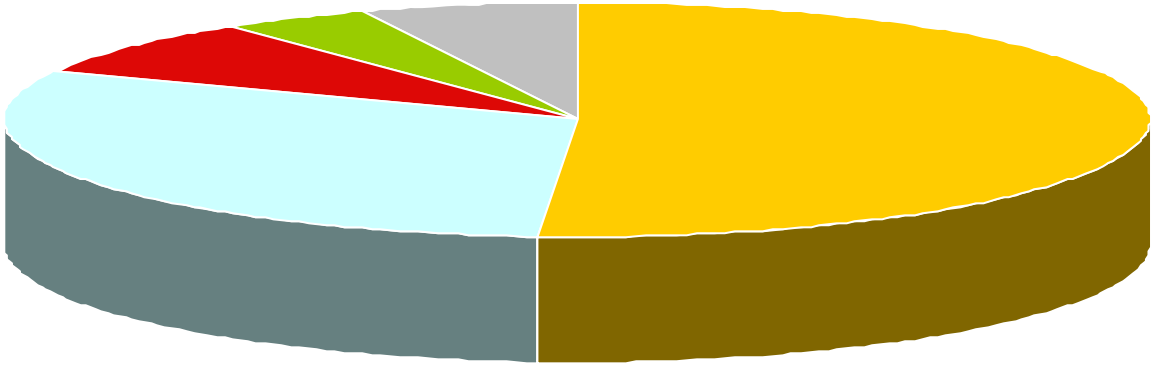


Figure 1. Evolution of the incidence of zygomycosis, France, 1997–2006. BMT, bone marrow transplantation.

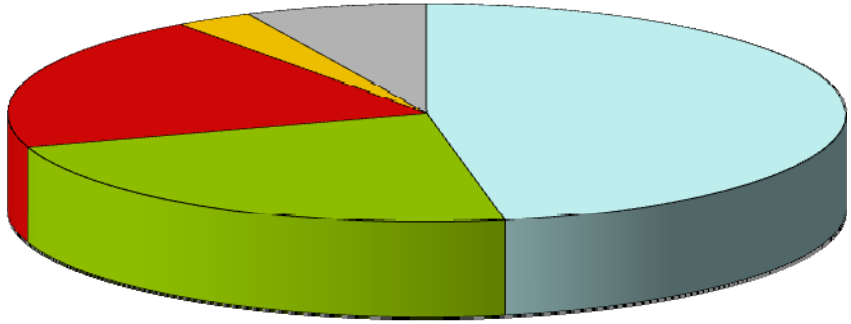
Candida isolates and candidemia in HSCT after prophylactic FCZ

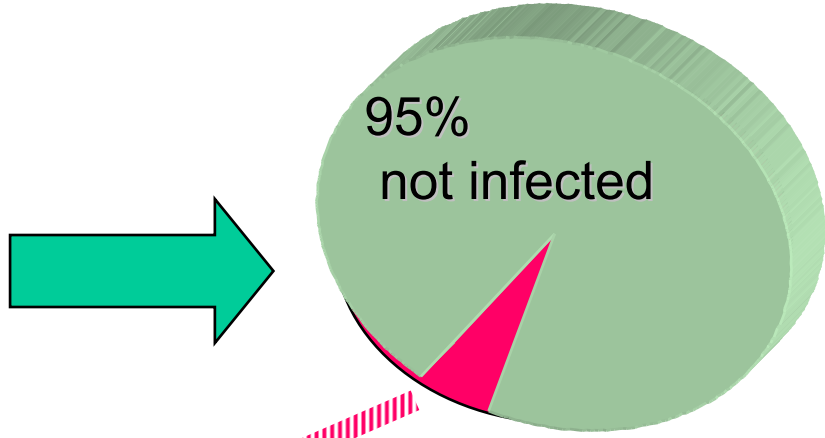
585 assessable patients

Oral colonization with *Candida*



34 (5%) candidemia





FCZ resistance

- albicans ⟷ 7%
- glabrata ⟷ 99%
- krusei
- parapsilosis
- others

Marr, JID 2000

Risk factors for FCZ resistant candidemia

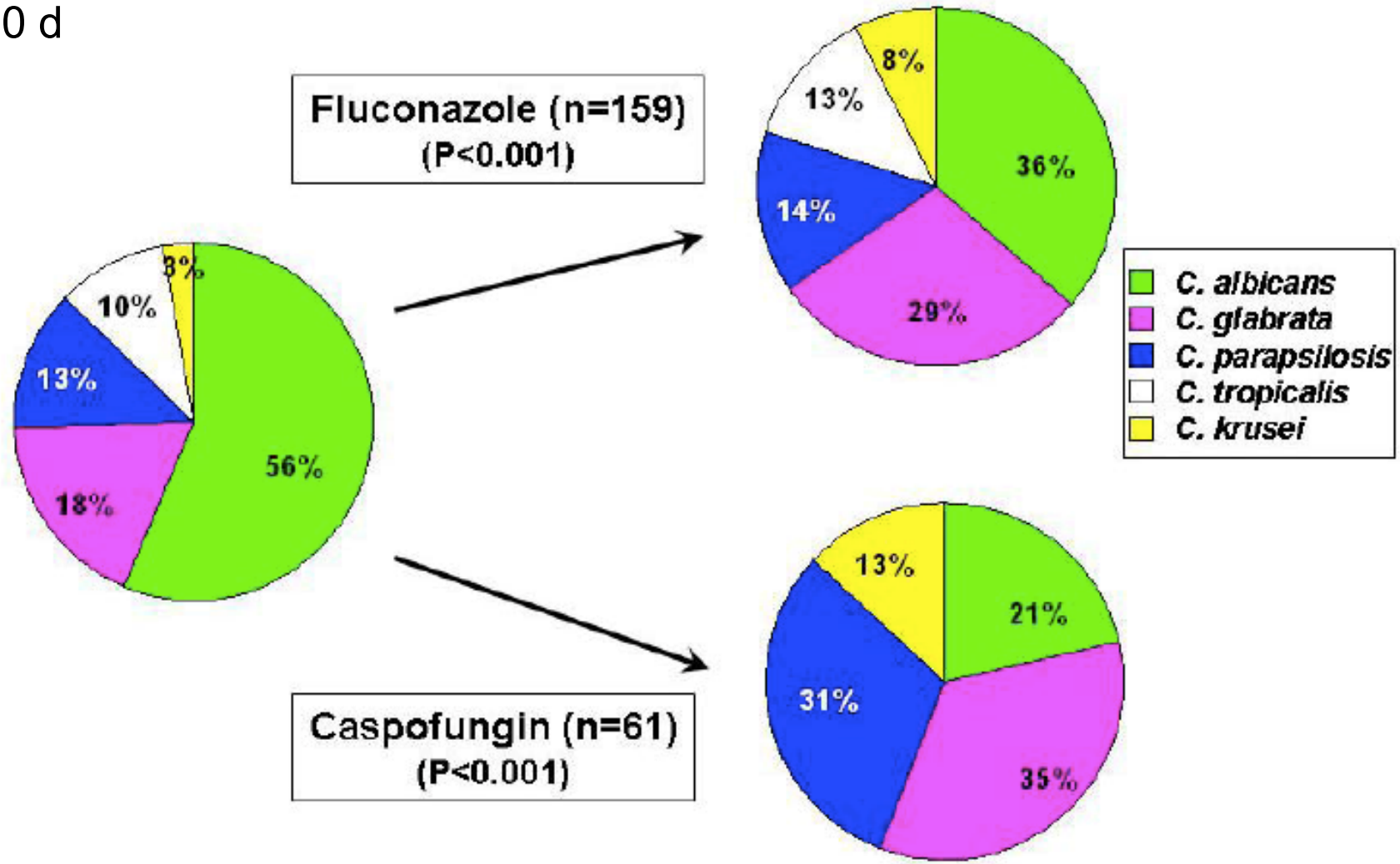
226 episodes; 30 FCZ resistant; CLSI; Seville 2004-2009

- ✓ Chronic renal failure: OR = 4.82 (1.47-15.88)
- ✓ Neutropenia: OR = 4.94 (1.50-16.20)
- ✓ **Fluconazole exposure (≥ 48h): OR = 5.09 (1.66-15.60)**

Garnacho-Montero, AAC 2010

Influence of recent FCZ or CAS exposure: distribution of *Candida* species during fungemia

Recent ≤ 30 d



Lortholary AAC 2010

Risk of fungemia due to caspofungin less susceptible *Candida* spp. in hematology

- ✓ Matched case-control study (51/102 pts) in Paris
- ✓ October 2002-February 2010
- ✓ Matching for center and date

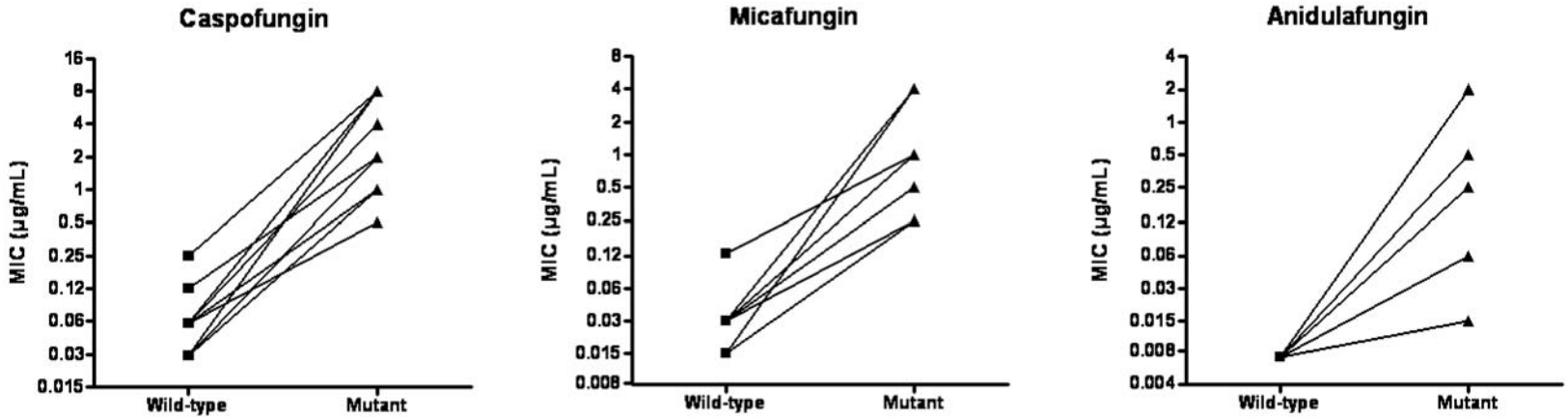
Blanchard, oral presentation, ECCMID 2011

Multivariate analysis	OR	CI 95%	*p*
Prior exposure to caspofungin (< 30 days)	5.25	[1.68-16.35]	0.004
Age at fungemia (≤ 65 yrs vs > 65 yrs)	3.27	[1.26-8.50]	0.015

Relationship between *C. parapsilosis* caspofungin MICs and consumption of caspofungin (Grenoble, France; 2004-2009, Fournier, unpublished data)

Emergence of infections due to *Candida* spp. with acquired echinocandin-resistance

- ✓ 20 episodes in patients previously (19/20) and/or currently (13/19) treated by caspofungin in France [median 27 d (10-270 d]
- ✓ 10 *C. glabrata*, 8 *C. albicans* and 2 *C. krusei*
- ✓ Caspofungin MIC≥0.5 mg/ml (range=0.5-8 µg/mL) (AM3, EUCAST)
- ✓ Mutations in Fksp sequence : cross resistance



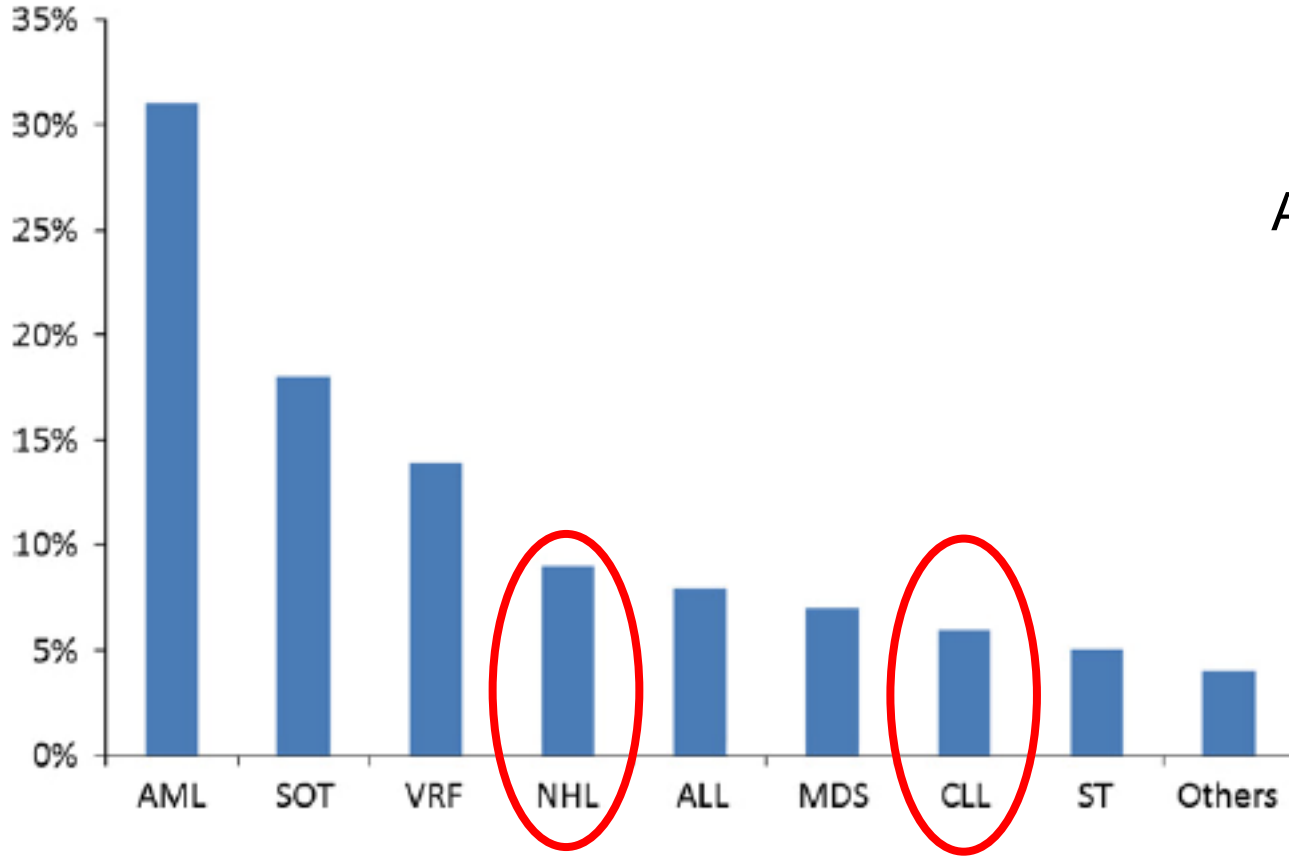
Same genotype

Dannaoui, ECCMID 2010; submitted

EMERGING HOSTS

- Chronic lymphoid malignancies
- Major role of diabetes
- Anti-TNF-α–treated patients
- Foreign devices
- Extreme ages
- Adults with primary immune deficiencies

New high-risk populations and mold infections

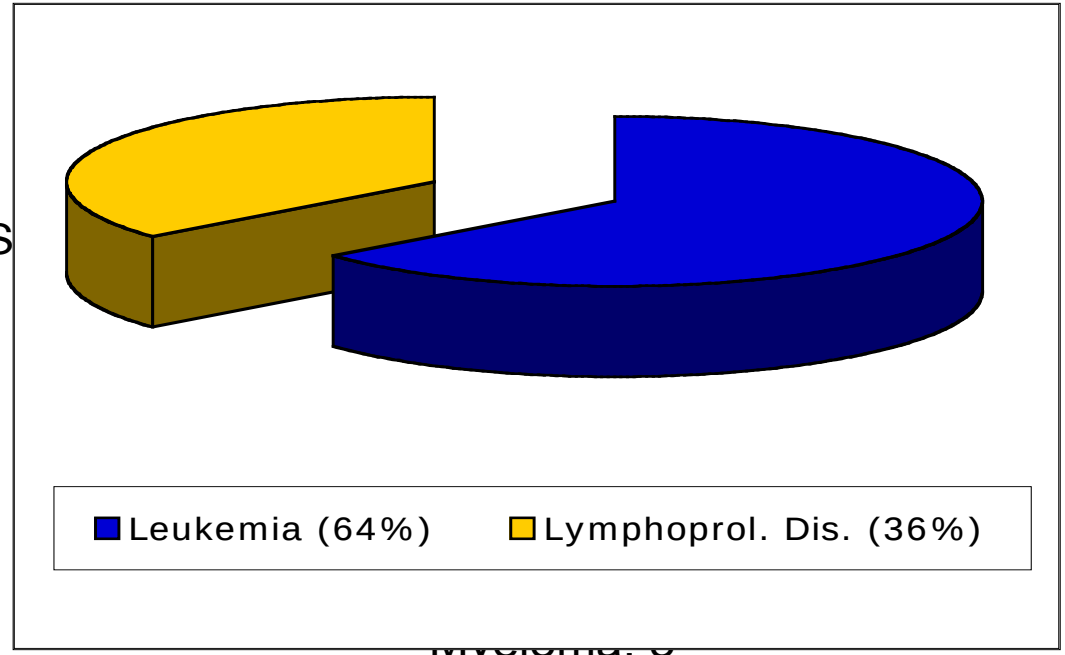


186 pts
Austrian Registry

Perkhofer Int J Antimicrob Agents 2010

New high risk populations and IA

Risk	n = 300
Acute leukemia	ALL 21
45%	
n=135	
Allo-HS	
28 %	
n=84	
Lymphoprolif. Diseases	Lymphoma: 42
29%	CLL: 26
n=87	Myeloma: 13
	Others: 4

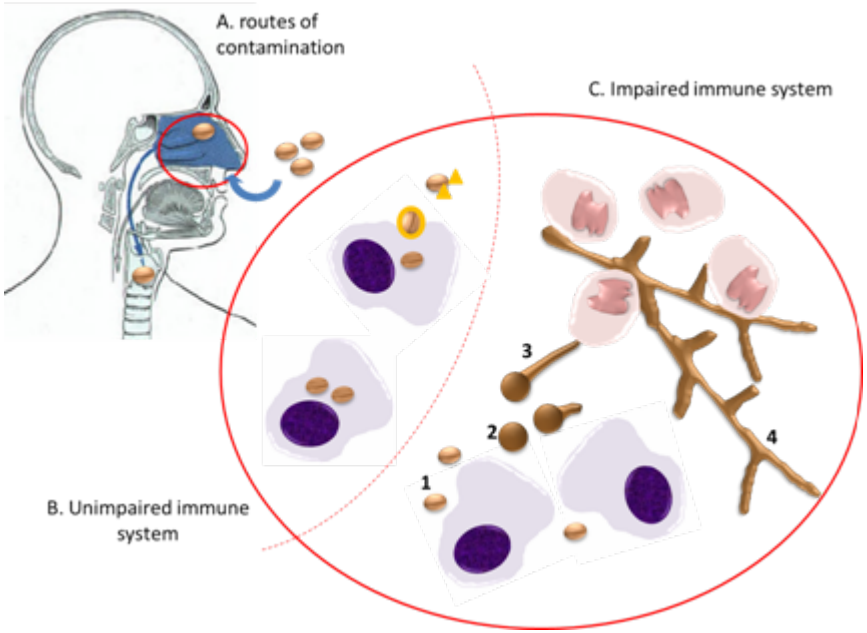


Purine analogs
Anti-CD52

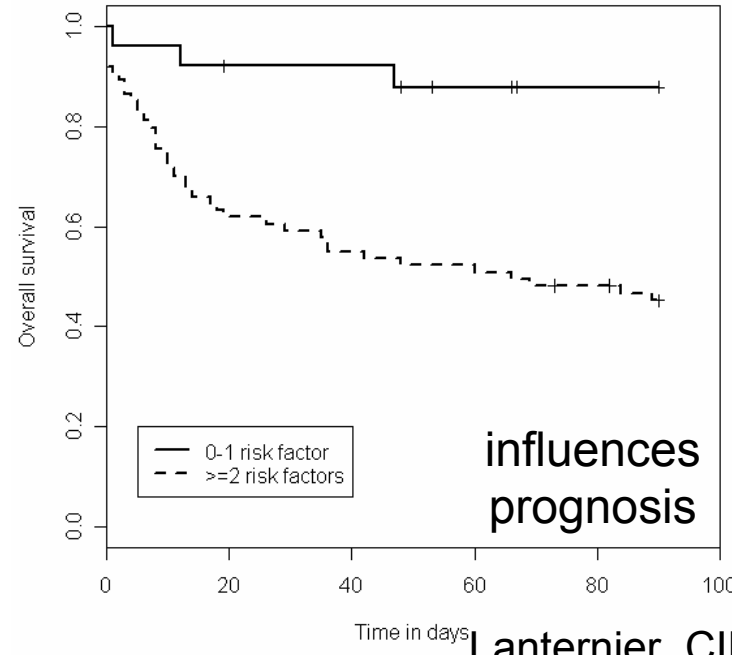
Lortholary, CMI April 2011 online

Diabetes and IFI today

- ✓ **41-49% of HSCT recipients with IFI** (Neofytos, CID 2009)
- ✓ **Independent risk factor of mucormycosis in leukemia and/or BMT and SOT** (Kontoyiannis JID 2005, Singh JID 2009)



- ✓ **9% annual increase of mucormycosis in diabetes** (Bitar EID 2009)
- ✓ **23% of 101 pts with mucormycosis in France (2005-2007)**



Lanternier, CID in press

Granulomatous infections in anti-TNF-α-treated patients

- ✓ **Infliximab (Remicade®; n = 197,000) or etanercept (Enbrel®; n = 113,000)**

Infection	No. of patients (no. of patients per 100,000 patients treated), by drug: Infliximab[a]	Etanercept[b]	P[c]
Aspergillosis	17 (8.63)	7 (6.19)	.243
Candidiasis	20 (10.15)		
Bartonellosis	1 (0.51)		
Coccidioidomycosis	11 (5.58)		
Cryptococcosis	10 (5.08)		
Histoplasmosis	37 (18.78)		
Legionellosis	1 (0.51)	0 (0)	.563
Leprosy	1 (0.51)	0 (0)	.563
Listeriosis	17 (8.63)	1 (0.88)	.0006
Nontuberculous mycobacterioses	22 (11.17)	7 (6.19)	.066
Nocardiosis	7 (3.55)	1 (0.88)	.090
Pneumocystosis	1 (0.51)	0 (0)	.563
Salmonellosis	0 (0)	2 (1.77)	.031
Toxoplasmosis	4 (2.03)	0 (0)	.101
Tuberculosis	106 (53.81)	32 (28.32)	<.0001
Total	255 (129.44)	68 (60.18)	<.0001

72 vs 28 % = first 3 months

Wallis CID 2004

Opportunistic infections in anti-TNF-α-treated patients: the Ratio Registry

- ✓ **45 cases in 43 patients**
  - **infliximab (n=29), adalimumab (n=10), etanercept (n=4)**
  - **Other diseases than colitis (n=35)**
  - **22% IFI (5 PCP, 3 aspergillosis, 2 cryptococcosis)**
  - **Infliximab ([OR] 17.96, 95% CI [4.45-72.46], p<0,0001) or adalimumab (OR 10.28, [2.35-44.94], p=0.002)**
  - **Steroid therapy >10 mg/d or iv bolus within one year (OR 5.65 [1.74-18.35], p=0.004)**

Other infections than tuberculosis/legionellosis

Salmon et al. Ann Rheum Dis 2011

Anti TNF and *Histoplasma capsulatum*

10 cases; 9 infliximab

1 wk-6 mo after initiation

9 ICU, 1 death

Lee, Arthritis Rheum 2002

Increased number of cases in USA (240 cases declared to FDA)

3 x more frequent than TB

Most frequent IFI in USA; mortality = 20%

Infliximab (x7) > Etanercept

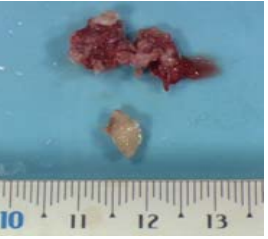
Pneumonia/dissemination (70-80%)

IRIS = 42% cases in Indianapolis

No role of screening (Ag/Ab)

Anti-TNF can be restarted if ATF ≥ 1yr without relaose

Hage et al. CID 2010

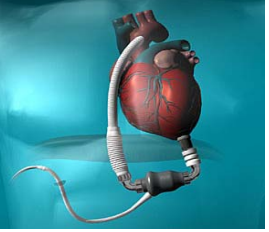


Proportion of devices among 30 cases of *Candida* endocarditis in France: 43.3%

Underlying cardiac disease	n (%)
Predisposing heart disease	17 (57)
Valvular prosthesis	10 (33)
Prior endocarditis*	8 (27)
Pace maker	2 (7)
Artificial heart	1 (3)
Congenital heart disease	1 (3)

*Median time, 1.5 year [15 days-10 years] before *Candida* endocarditis

Lefort et al. Mycendo Prospective Study, ICAAC 2009 & 2010; submitted



Ventricular-Assist Device infections

36% VAD become infected

IFI: 21% VAD infections

70% fluconazole prophylaxis!

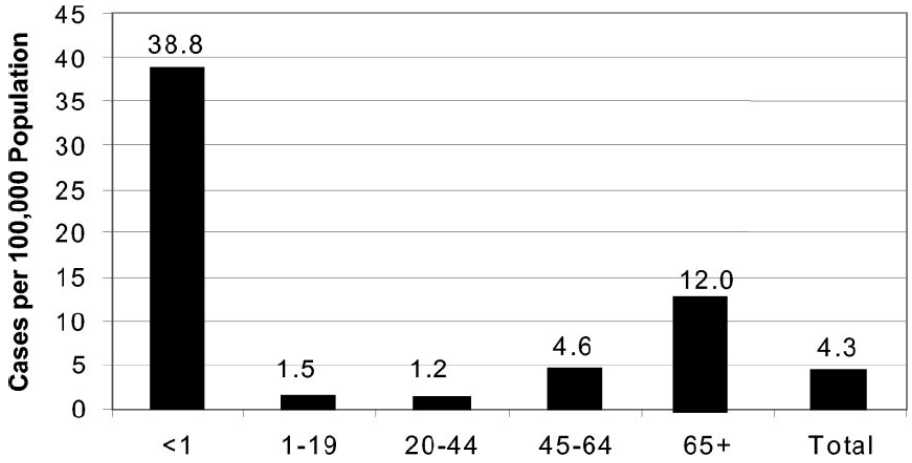
Total parenteral nutrition: OR = 6.95

Table 1. Microbiology of 108 Patients with Ventricular-Assist Device (VAD) Infections

Microorganism	No (%) of total isolates (n = 209)	Source of microbiological isolates			
		Driveline (n = 67)	Pocket (n = 55)	Bloodstream (n = 68)	Infective endocardit (n = 19)
Bacterial isolates					
All	178 (85.2)	62	49	53	14
Staphylococcus aureus	44 (21.1)	16	11	13	4
MRSA	23 (11)	7	7	8	1
Coagulase-negative staphylococci	40 (19.1)	14	8	15	3
Enterococcus species	30 (14.4)	5	12	12	1
VRE	19 (9.1)	1	10	8	0
Streptococcus viridans	3 (1.4)	1	2	0	0
Corynebacterium species	2 (1)	0	1	0	1
Diptheroids	1 (0.5)	1	0	0	0
Bacillus species	1 (0.5)	0	0	0	1
Lactobacillus species	1 (0.5)	0	1	0	0
Pseudomonas aeruginosa	21 (10)	11	3	5	2
Klebsiella pneumoniae	9 (4.3)	2	3	3	1
Enterobacter cloacae	7 (3.3)	3	2	2	
Citrobacter freundi	4 (1.9)	1	2	1	0
Serratia marsescens	4 (1.9)	1	1	2	0
Proteus mirabilis	2 (1)	1	1	0	0
Escherichia coli	1 (0.5)	1	0	0	0
Bacteroides species	6 (2.9)	3	2	0	1
Eikinella species	1 (0.5)	1	0	0	0
Prevotella species	1 (0.5)	1	0	0	0
Fungal isolates					
All	31 (14.8)	5	6	15	5
Candida albicans	14 (6.7)	3	3	5	3
Candida glabrata	7 (3.3)	0	2	4	1
Candida kruseii	6 (2.9)	2	1	2	1
Candida parapsilosis	3 (1.4)	0	0	3	0
Candida antigen positive[a]	1 (0.5)	0	0	1	0

Aslam CID 2010

Candidemia in children: « not just little adults »



- ✓ Neonatal age: independent factor of non-*albicans* species (OR = 4.42)

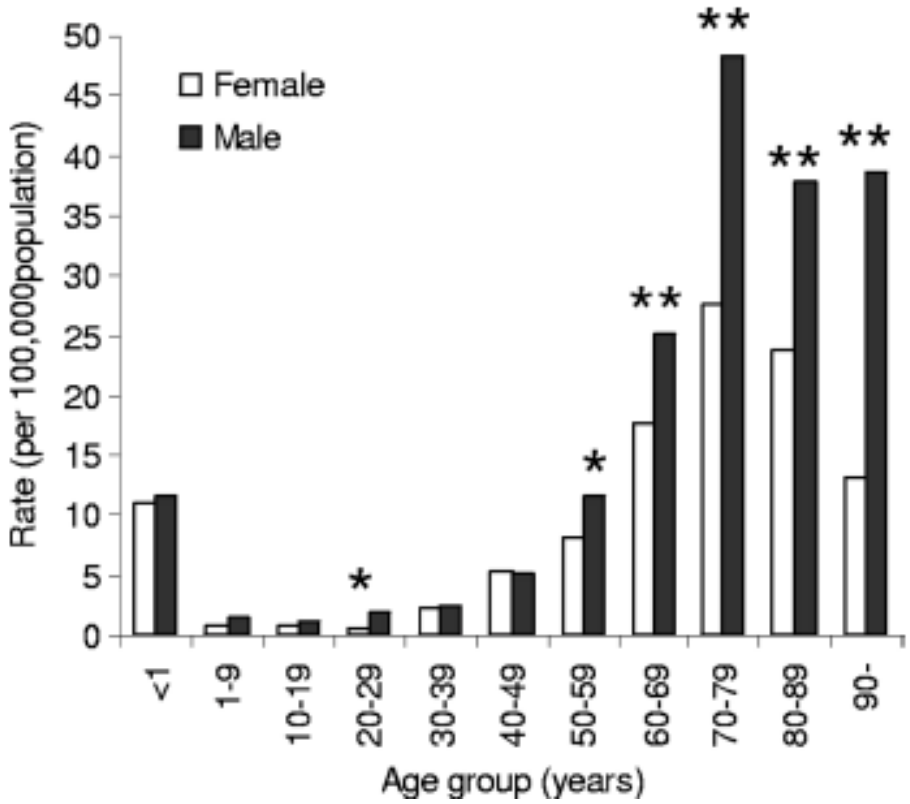
Barcelona, 2002-2003. Almirante JCM 2005; Rodriguez CMI 2010

1005 cases	Neonat	Children	Adults
Incidence /100.000	4.4	0.9	1.8
C. parapsi %	42	38	15
D30 Surv %	78	90	70

- ✓ Median age: 9 mo
- ✓ 36% < 3 mo
- ✓ *C. parapsilosis*: 43%
- ✓ *C. albicans*: 26%

3yrs pop-based Australia study. Blyth Pediatrics 2009 Children's Hosp NY, 2002-2006. Neu, PIDJ 2009

Elderly patients with candidemia in Europe



Denmark

Age (yrs)	≤ 59	60-69	70-79	≥ 80
% *C. glabrata*	≤ 20	23	22	29

Paris

Age (yrs)	15-44	45-65	> 65
D30 death	27.2	39.8	48.6
% < D8	54.3	57.2	56.6

Arendrup, 2004-2009 Denmark, JCM 2011; Yeast Program, unpublished

Primary immune deficiency patients become older

Carneiro-Sampaio IAI 2007

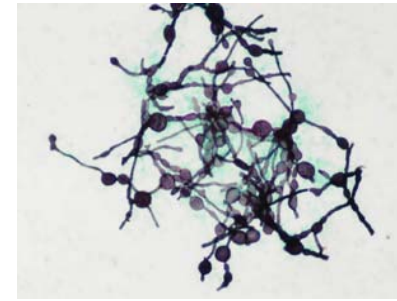
TABLE 5. Reported clinical associations between PIDs and different fungal infections

PID associated with indicated fungus:			
Candida	*Aspergillus fumigatus*	*Cryptococcus neoformans*	*Histoplasma capsulatum*
APECED (2, 6)	Chronic granulomatous disease (3, 15, 113)	Idiopathic CD4 lymphocytopenia (103)	Idiopathic CD4 lymphocytopenia (103)
Other forms of chronic mucocutaneous candidiasis (45)	Hyper-IgE syndrome (3, 50)	Hyper-IgE syndrome (10, 50)	XL hyper-IgM syndrome (CD40L deficiency) (114)
Hyper-IgE syndrome (10, 50, 65)	SCID[a] (117)		Hyper-IgE syndrome (50)
SCID (11, 12, 105)	Leukocyte adhesion deficiencies (LADs) (97)		Autosomal dominant form of IFN-γ receptor 1 deficiency[a] (118)
MHC-II deficiency (57)	Idiopathic CD4 lymphocytopenia (45)		
Idiopathic CD4 lymphocytopenia (103)			
XL-EDA-ID (defects of NEMO) (60, 83)			
Myeloperoxidase deficiency in diabetic patients (97)			
Wiskott-Aldrich syndrome (106)			

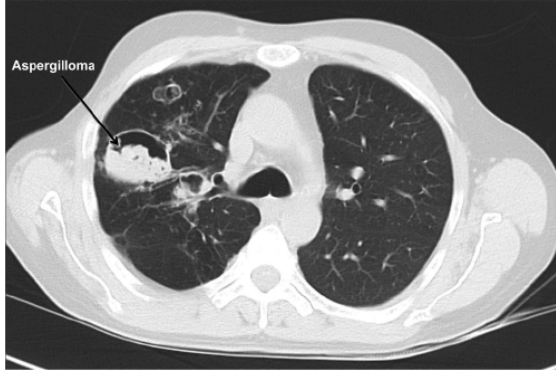
Aspergillosis = 1st cause of death during CGD [Winkelstein, Medicine 2000]

IFI during CGD

- ✓ CEREDIH, France, 1976-2008 [Beauté, PIDJ 2010]
  - Incidence IFI 0.040/pts-years
  - 42.6% (66/155) ≥ 1 IFI episode
  - Median age at IFI diagnosis = 6.5 yrs (3.3-11.3).
  - *Aspergillus* spp. = 1/3 IFI
  - Reduced survival if IFI (Log-Rank=0,04).



Hyper-IgE syndrome



NIH experience

- ✓ Abscesses + pneumonia + hyper IgE = 77%
- ✓ CMC: 25/30 (83%)
- ✓ IFI : 14/30 (47%)
  - Aspergillosis: 9/30 (30%)
  - Invasive candidiasis: 2/30
  - PCP : 2/30
  - Cryptococcosis : 1

CEREDIH experience (France)

- ✓ 59 pts with autosomal dominant STAT 3 deficiency
- ✓ CMC: 50/59 (85%)
  - Oral = 64%
  - Onychomycosis = 56%
  - Skin = 16%
- ✓ Aspergillosis: 13/59 (22%)
- ✓ PCP: 2
- ✓ Cutaneous cryptococcosis: 1

Grimbacher. NEJM 1999

Chandesris, Submitted

IFI do not exist in « immunocompetent » hosts !
Immunodeficient hosts are not created equals !

Recent important works from Europe…

Royal Free & Univ College, London
Univ Hosp of South Manchester
Univ of Lausanne
Radboud Univ, Nijmegen
Leiden Univ Med Centre
Necker Enfants malades, Paris

Role of genetic susceptibility to IFI

SOME EMERGING IFI/FUNGI IN EUROPE

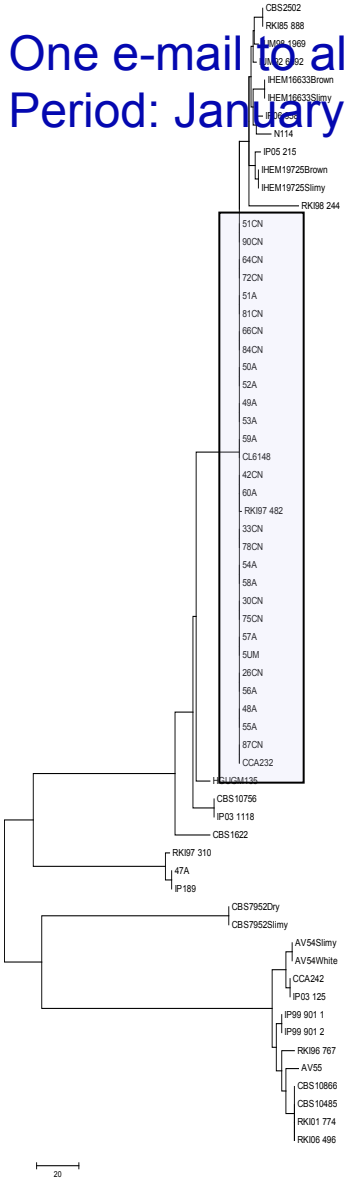
Chronic pulmonary aspergillosis

- ✓ **Chronic lung diseases + symptoms for months**
  - Weight loss/fatigue
  - Chronic cough/chest pain
  - Upper lobe cavitary or fibrotic disease
- ✓ **Underlying diseases** (126 patients, Manchester)
  - Previous tuberculosis : 15.3%
  - Non-tuberculous mycobacterial infection : 14.9%
  - Others: ABPA, COPD and/or emphysema, pneumothorax & prior lung cancer
- ✓ **50% molecular detection of triazole resistance** in non culturable *A. fumigatus* from CPA patients

Denning, CID 2003; Smith Eur Respir J 2011; Denning CID 2011

A Mediterranean *C. gattii* clade?

One e-mail to all national mycological societies
Period: January 2007 – December 2008



Spain and Greece MATα and in Italy MAT**a**

2 patients, never travelled outside Spain (Madrid/Alicante) plus 3 small outbreaks in goats

1 patient, never travelled outside Italy (Bari) plus environmental sampling

2 patients, never travelled outside Greece

Kindly provided by Ferry Hagen & Teun Boekhout

Autochtonous emergence of *Cladophialophora bantiana* infections in South France

NRCMA, unpublished data

Emericella quadrilineata as Cause of Invasive Aspergillosis

Paul E. Verweij,* János Varga,†‡ Jos Houbraken,† Antonius J.M.M. Rijs,* Frans M. VerduynLunel,* Nicole M.A. Blijlevens,* Yvonne R. Shea,§ Steven M. Holland,§ Adilia Warris,* Willem J. G. Melchers,* and Robert A. Samson†

- ✓ **3 cases during CGD**

Table. Antifungal activities against *Emericella nidulans* and *E. quadrilineata*

Drug	MIC, mean		Significance*
	E. nidulans (n = 12)	*E. quadrilineata* (n = 12)	
Amphotericin B	2.5	0.5	p<0.05
Itraconazole	0.07	0.13	NS
Voriconazole	0.26	0.39	p<0.05
Posaconazole	0.25	0.22	p<0.05
Caspofungin†	0.32	1.83	p<0.05
Terbinafine	0.01	0.009	NS

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 14, No. 4, April 2008

Emergence of *Geosmithia argillacea* in CGD patients

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

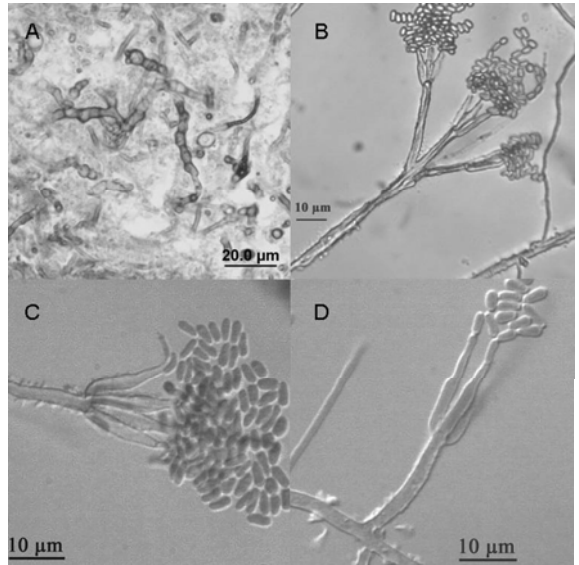
- ✓ **Two cases of *G. argillacea* inf**
- ✓ **Prior ITZ ± VCZ**
- ✓ **Disseminated infections**
- ✓ **Multiply in vitro resistance & clinical failure**

Machouart JCM Epub Jan 2011

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

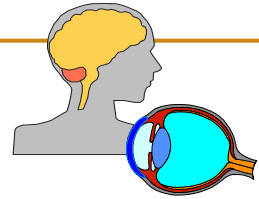
- ✓ **7 cases of *G. argillacea* inf**
- ✓ **5 previously identified as *Paecilomyces variotii***
- ✓ **Disseminated infections**
- ✓ **3 deaths**

De Ravin CID March 2011



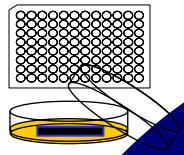
IFI in our hospitals today: more individualized approach

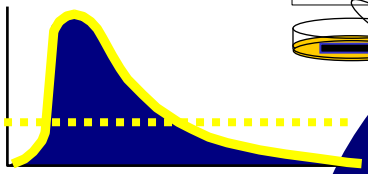
Drug interactions?
Prior therapies?



Sanctuary site involvement?

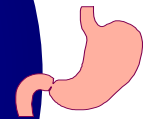
Resistance?





PK/PD & Drug dosing?

Hepatic & renal function?

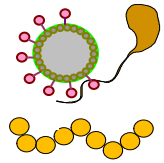


GI function?

Pathogen virulence?

Infected hardware or catheters?

Diagnostic certainty?



Concomitant Infections?

Immunosuppression & reconstitution?

Dose, timing, intensity of Immunosuppressive therapy?

Adapted from Kontoyiannis D.

Unmet medical needs in medical mycology in Europe

- ✓ **Large epidemiological [but exhaustive] surveys**
  - Nationwide, ECMM, ISHAM, registries (Fungiscope, …)
- ✓ **Better diagnostic and monitoring tools**
  - **Limits of antigen detection:**
    - GXM in non HIV cryptococcosis/GM in non neutropenic hosts with IA
    - More works on antigens as monitoring tools **(when stopping ATF?)**
  - **PCRs: from research labs to clinical labs**
  - **Reduced time for final diagnosis: implement mass spectrometry**
  - **Evaluation of new imaging tools**

Unmet medical needs in medical mycology in Europe

- ✓ **Individualize prognostic scores in order to…**
- ✓ **Improve therapeutic strategies: ESCMID guidelines**
  - *Candida* guidelines (Ullmann & Committee, ECCMID 2011)
- ✓ **Better evaluate impact of antifungal use (ECDC?)**
- ✓ **Promote Medical Mycology Centers for Excellence in Europe**
  - Highly specialized care/research/mycology courses
  - Better allocation of health care resources and research budgets
  - ESCMID granted MMCE?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