Neutropénies fébriles: stratégie pratique antifongique

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Service de maladies infectieuses
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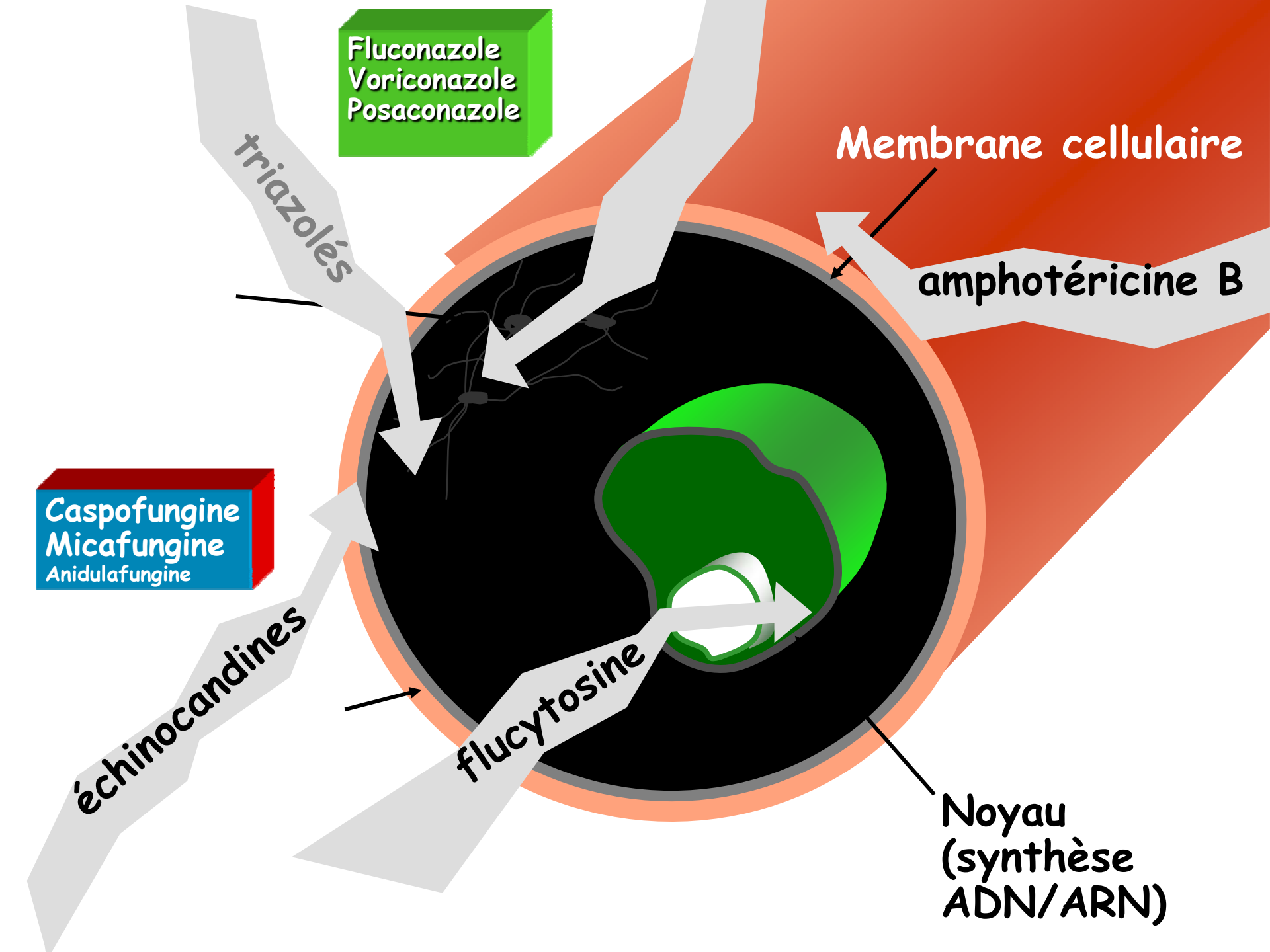
- Principaux antifongiques: mode d'action et spectre
- Epidémiologie des IFI en hématologie
- Prophylaxie antifongique
- Prophylaxie et émergence de résistances
- Traitement préemptif
- Traitement empirique
- Traitement curatif


Fluconazole
Voriconazole
Posaconazole
triazolés
Membrane cellulaire
amphotéricine B
Caspofungine
Micafungine
Anidulafungine
échinocandines
flucytosine
Noyau
(synthèse
ADN/ARN)

IMPORTANCE DU SPECTRE ANTIFONGIQUE

	Polyène	FLC	ITZ	VRZ	POS	Candines
C. albicans	+	+	+	+	+	+
C krusei et glabrata	+	-	-	+	+	+
C. parapsilosis et guillermondi	+	+	+	+	+	+/-
Cryptococcus neof	+	+	+	+	+	-
Aspergillus spp	+	-	+	+	+	+
Zygomycetes spp	+	-	-	-	+	-
Fusarium spp	+	-	-	+/-	+/-	-

EPIDEMIOLOGIE DES IFI ET HSCT

Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database

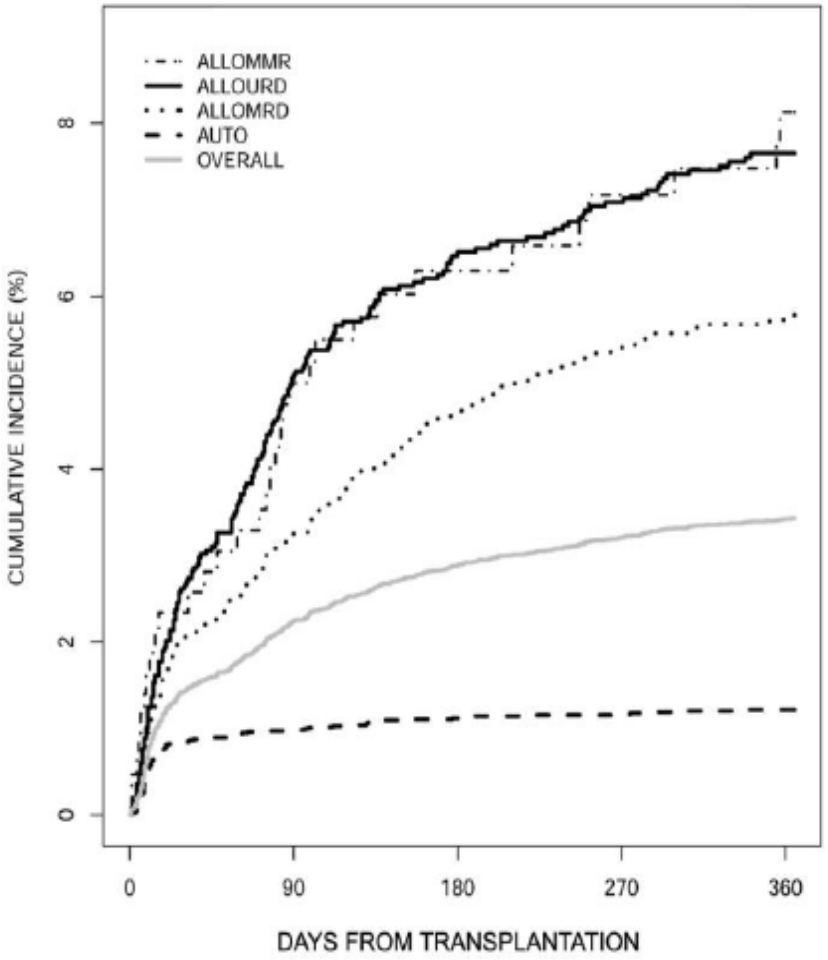
Dimitrios P. Kontoyiannis, Kieren A. Marr, Benjamin J. Park, Barbara D. Alexander, Elias J. Anaissie, Thomas J. Walsh, James Ito, David R. Andes, John W. Baddley, Janice M. Brown, Lisa M. Brumble, Alison G. Freifeld, Susan Hadley, Loreen A. Herwaldt, Carol A. Kauffman, Katherine Knapp, G. Marshall Lyon,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

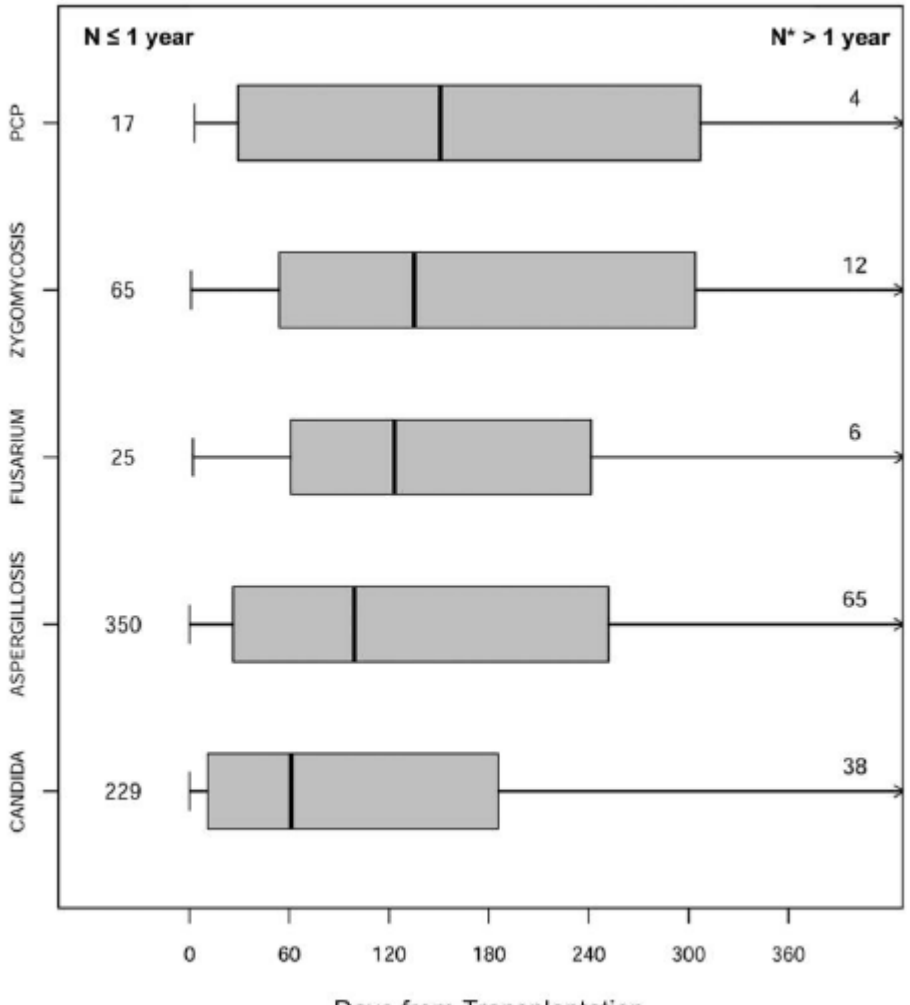
Clinical Infectious Diseases 2010;50:1091–1100

1058-4838/2010/5008-0003$15.00
DOI: 10.1086/651263

- 23 centres de transplantation aux US
- IFI probables ou prouvées
- 2001-2006
- 983IFI, 875 patients
  - Aspergillose invasive (43%), J99
    - *A. fumigatus* (45%)
  - Candidose invasive (28%), J61
    - *C. glabrata* (32%), *C. albicans* (19%), *C. parapsilosis* (16%)
  - Zygomycose (8%)

EPIDEMIOLOGIE DES IFI ET HSCT





Clinical Infectious Diseases 2010;50:1091–1100

1058-4838/2010/5008-0003$15.00
DOI: 10.1086/651263

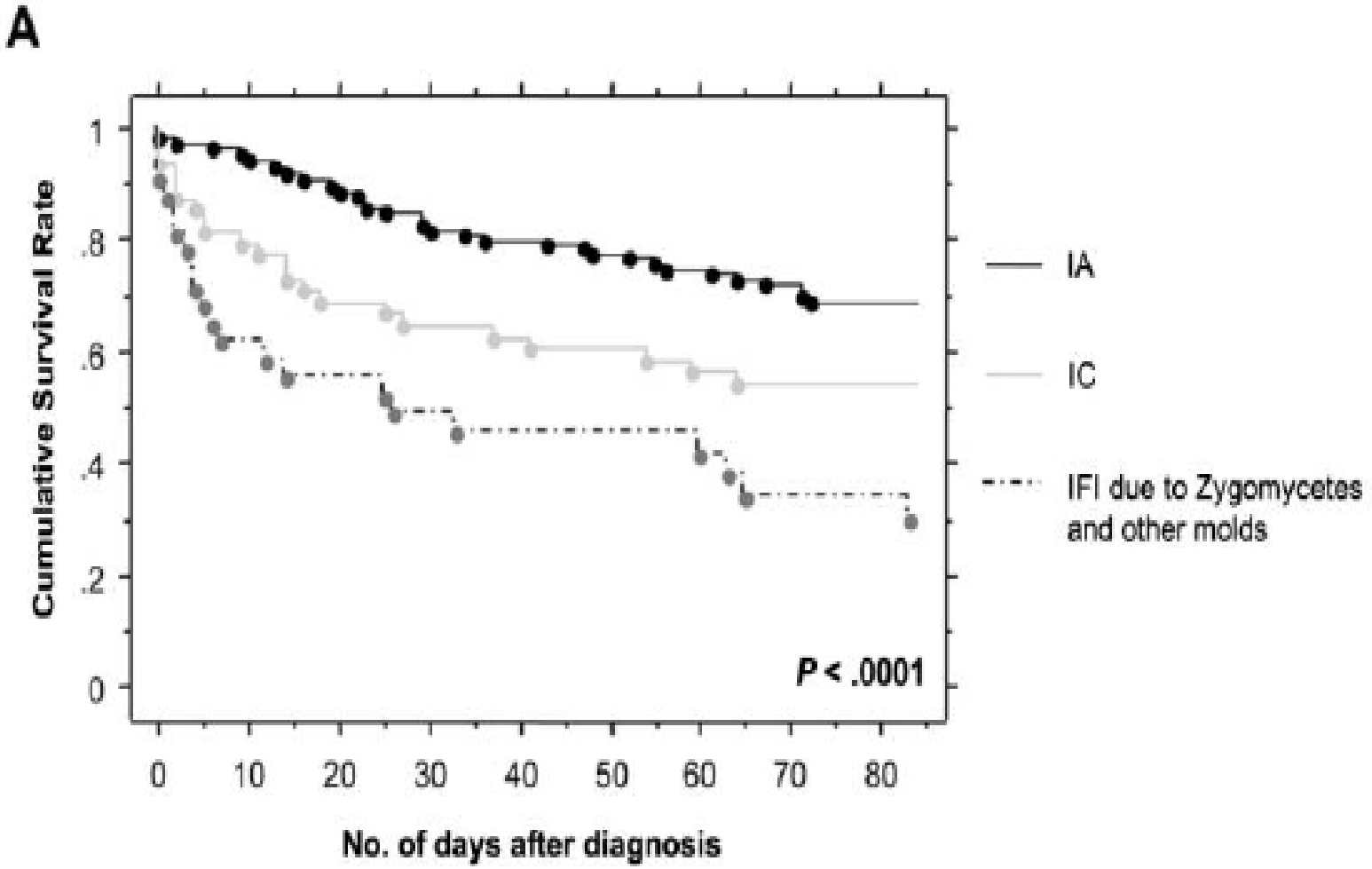
EPIDEMIOLOGIE DES IFI ET HSCT

Epidemiology and Outcome of Invasive Fungal Infection in Adult Hematopoietic Stem Cell Transplant Recipients: Analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance Registry

D. Neofytos,[1,2] D. Horn,[2] E. Anaissie,[3] W. Steinbach,[4] A. Olyaei,[5] J. Fishman,[6] M. Pfaller,[7] C. Chang,[9] K. Webster,[10,11] and K. Marr[1,8]

- 2004-2007
- 13 centres US
- 234 patients, 250 IFI
  - Aspergillose invasive, 59%, mortalité 21% S6
  - Candidose invasive, 25%
  - Zygomycoses 7%

EPIDEMIOLOGIE DES IFI ET HSCT



INFLUENCE DE L'EXPOSITION A LA CASPOFUNGINE ET AU FLUCONAZOLE SUR L'EPIDEMIOLOGIE DES CANDIDEMIES

- Ile de France; 2002-2009
- Isolats de candidémies
- 2618 isolats, 2441 patients
- 18% hématologie
- Enregistrement d'une exposition au fluconazole et/ou à la caspofungine dans les 30 jours précédents (232, 9.5%)
- Résistance au FLC: CMI $\geq$ 8 mg/L
- Résistance à la CAS: CMI $\geq$ 0.5 mg/L

Lortholary, AAC 2010

Répartition des espèces

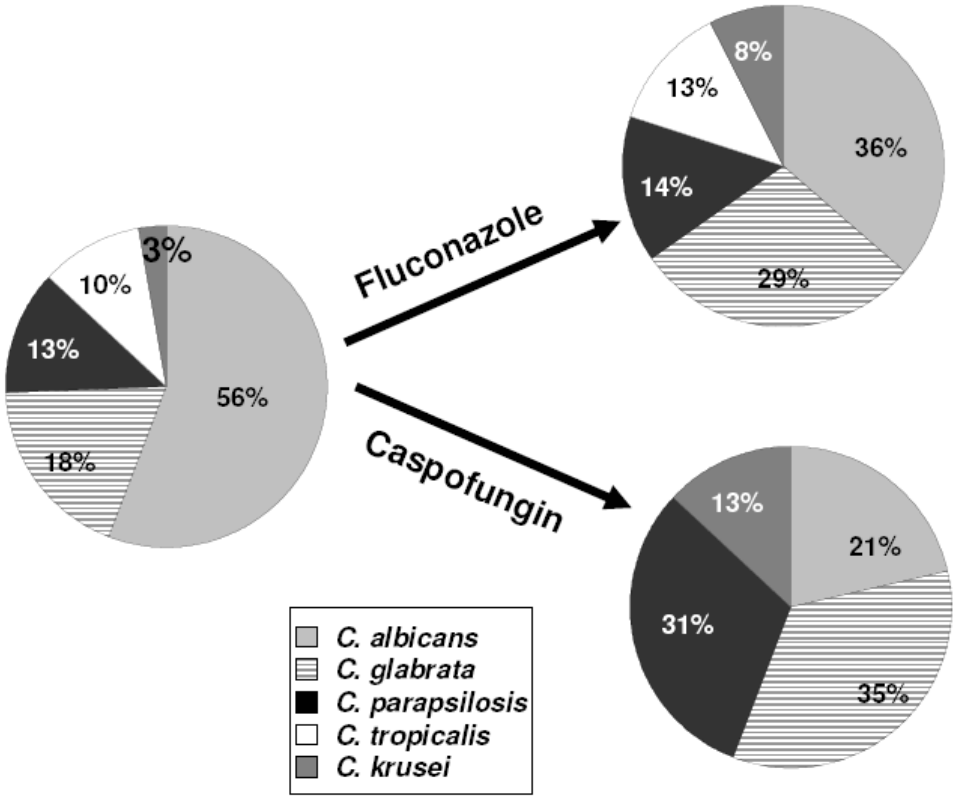


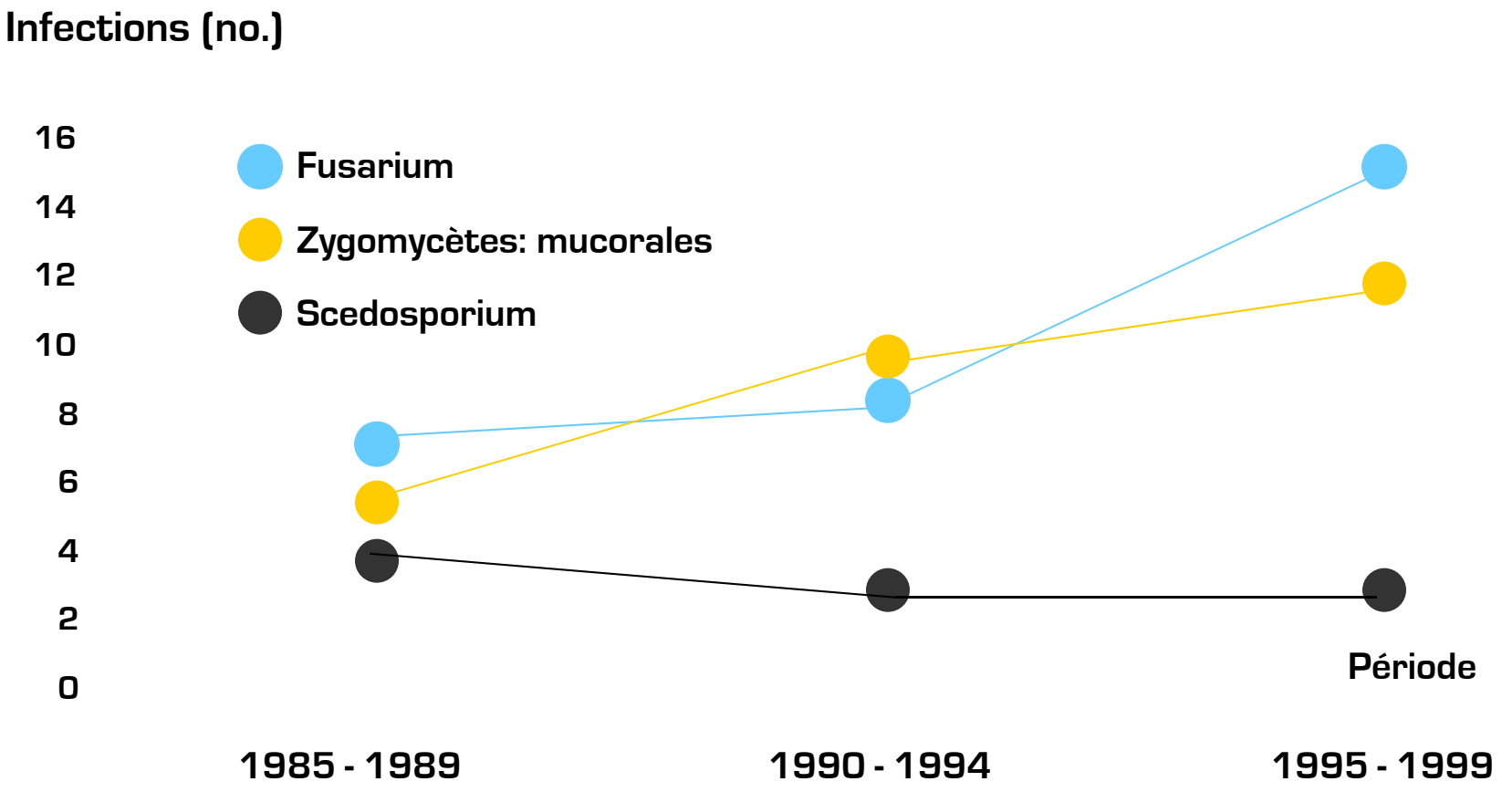
Table 1: Antifungal susceptibility of the 5 more frequent *Candida* species responsible for bloodstream infections according to recent (<30 days) exposure to fluconazole or caspofungin prior to diagnosis of fungemia (incident episode and first recurrence included)

	No preexposure recorded		Preexposure recorded		
	N	GMIC[a] (mg/L) [95% CI]	N	GMIC[a] (mg/L) [95% CI]	*P*[b]
Exposure to fluconazole					
Total	2289	0.77 [0.71-0.83]	159	2.31 [1.65-3.23]	< 0.001
C. albicans	1291	0.24 [0.23-0.24]	58	0.36 [0.25-0.51]	0.053
C. glabrata	413	13.97 [12.59-15.50]	46	18.05 [13.19-24.70]	0.129
C. parapsilosis	295	0.97 [0.86-1.08]	23	1.62 [0.99-2.64]	0.015
C. tropicalis	226	0.84 [0.70-1.00]	20	1.52 [0.76-3.01]	0.040
C. krusei	64	34.15 [29.88-39.02]	12	28.51 [10.78-75.41]	0.402
Exposure to caspofungin					
Total	1920	0.07 [0.07-0.08]	61	0.16 [0.12-0.22]	< 0.001
C. albicans	993	0.05 [0.05-0.05]	13	0.09 [0.04-0.22]	0.252
C. glabrata	365	0.07 [0.07-0.08]	21	0.12 [0.08-0.19]	0.418
C. parapsilosis	299	0.28 [0.26-0.31]	19	0.32 [0.23-0.45]	0.893
C. tropicalis	199	0.06 [0.05-0.06]	0		
C. krusei	64	0.15 [0.13-0.17]	8	0.19 [0.11-0.33]	0.571

[a] Geometric mean of minimum inhibitory concentration

[b] Mann-Whitney test

Émergence des infections à champignons filamenteux après allogreffe de moelle



Marr KA et al, Clin Infect Dis 2002

Emergence des zygomycoses en France

- 1997-2006
- 2 sources de données:
  - CNRMA
  - PMSI
- 547 cas
- Incidence: 0,9/ 10^6 /yr
- 0,7 cas/10^6 1997
- 1,2 cas/10^6 2006

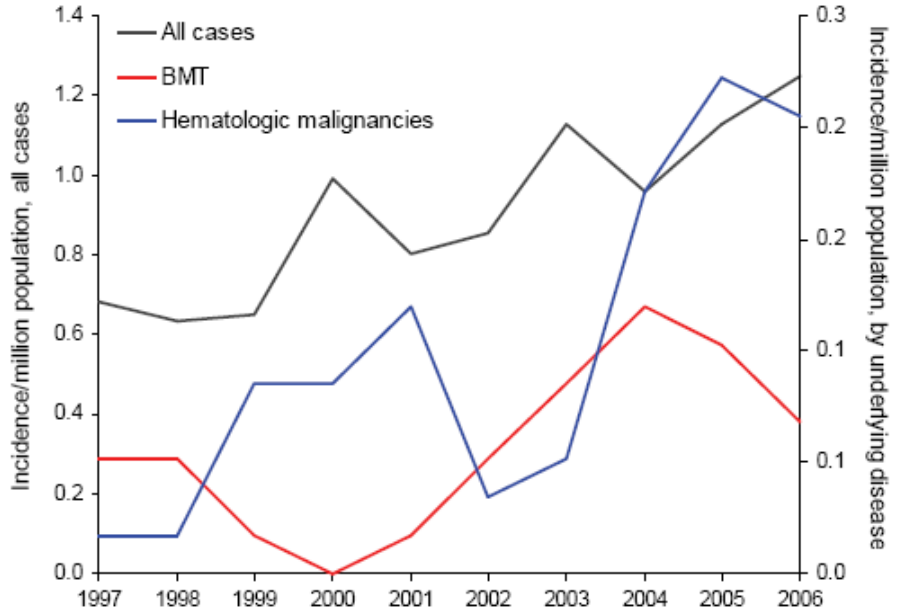
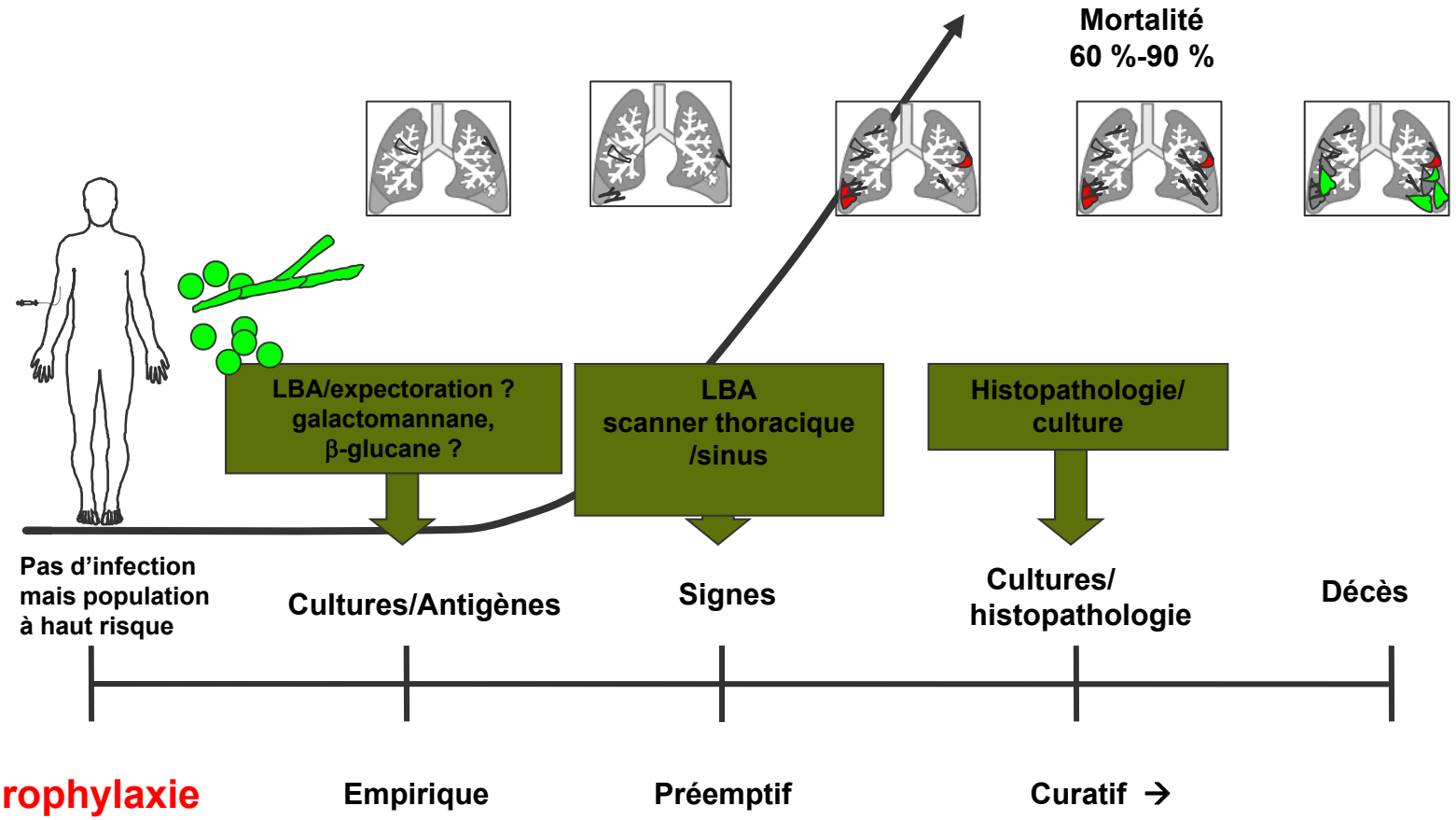


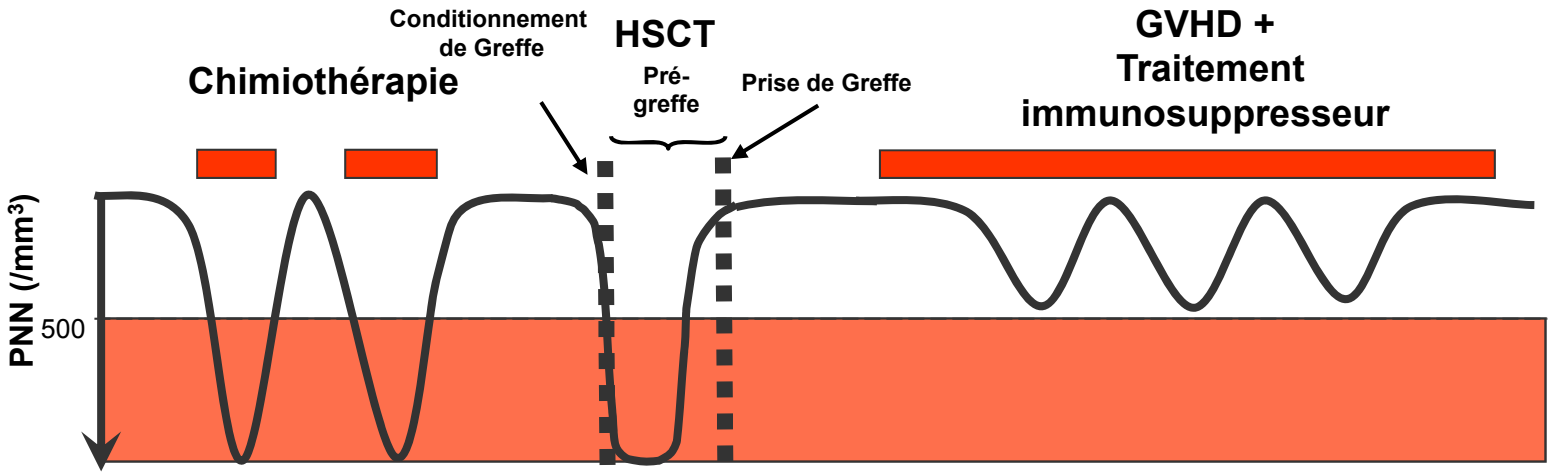
Figure 1. Evolution of the incidence of zygomycosis, France, 1997–2006. BMT, bone marrow transplantation.

Bitar D, EID 2009

Différentes phases thérapeutiques dans l'aspergillose invasive



PROPHYLAXIE AF: POUR QUI?
HEMOPATHIES MALIGNES/GVHD



1. Jantunen E *et al*. Incidence and risk factors for invasive fungal infections in allogeneic BMT recipients. Bone Marrow Transplant 1997;19 : 801-8.

ALLOGREFFE
FLUCONAZOLE: PROPHYLAXIE

Prophylaxie après greffe de moelle (prospectif, randomisé, double-aveugle, n=300)

Résultats	**FCZ 400**	**Pbo**	***p***
IF Systémiques	7%	18%	0.004
Infections à *C albicans*	0%	18%	< 0.001
IF superficielles	↓ Incidence		< 0.001
Colonisation fongique	↓ incidence		0.037
Ampho B en empirique	↓ utilisation		0.005
Décès	31	52	0.004

Slavin MA et al. *J Infect Dis. 1995*

ALLOGREFFE
ITRACONAZOLE: PROPHYLAXIE

Prophylaxie des receveurs d'allogreffe de CSH (prospectif, randomisé, ouvert; n=299)

Résultats	**ITRA**	**FLU**	***p***
IFI prouvées ou probables	7%	15%	0.03
Infections à filamenteux	5%	12%	0.03
Candidémies	3%	2%	0.69

Marr KA et al. *Blood 2004*

ALLOGREFFE
MICAFUNGINE: PROPHYLAXIE

Prophylaxie des IFI : receveurs de CSH neutropéniques

Succès = Pas d'IFI prouvée, probable ou possible au cours de la prophylaxie + 4 semaines après traitement (prospectif, randomisé, double aveugle; n= 882)

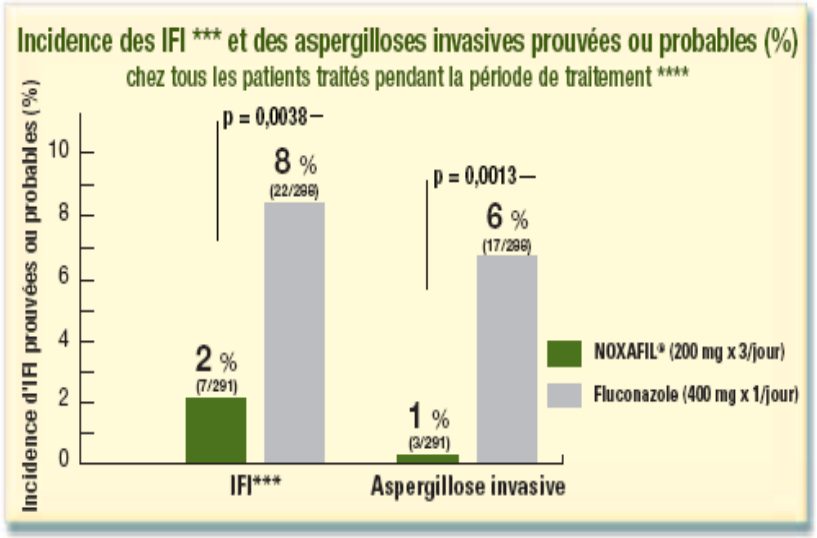
Résultats (1)	**MICA**	**FLU**	***p***
Succès global	80%	74%	0.03
Emergence d'infections			
- Candida	4	2	
- *Aspergillus*	1	7	0.071
- *Fusarium* spp	1	2	
- *Zygomycètes*	1	0	
Traitement empirique	15.1%	21.4%	0.024

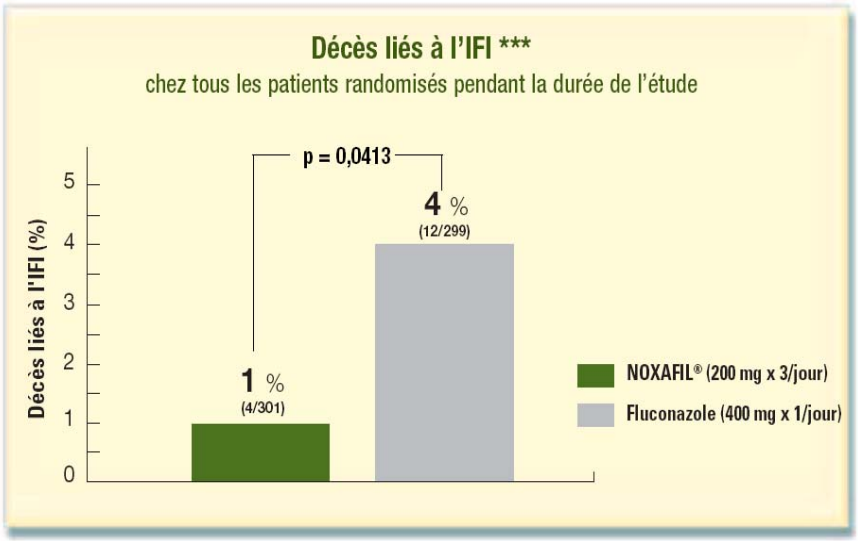
Pas de différence de mortalité

van Burik JA et al. *Clin Infect Dis. 2004*

ALLOGREFFE et GVH AIGUE (2-4) OU CHRONIQUE EXTENSIVE
POSACONAZOLE: PROPHYLAXIE

301 (PCZ) vs. 299 patients (FCZ)





Baisse significative de l'incidence des IFI et des AI *vs* fluconazole pendant la période de traitement

Proportion des décès liés aux IFI significativement inférieure dans le groupe posaconazole comparé au groupe fluconazole

Fréquence des effets indésirables comparable

Les agents pathogènes en cause retrouvés en dehors des *Aspergillus* spp étaient *Candida* spp, *Rhizomucor* spp, *Scedosporium prolificans, Pseudallescheria boydii* et *Trichosporon* sp.

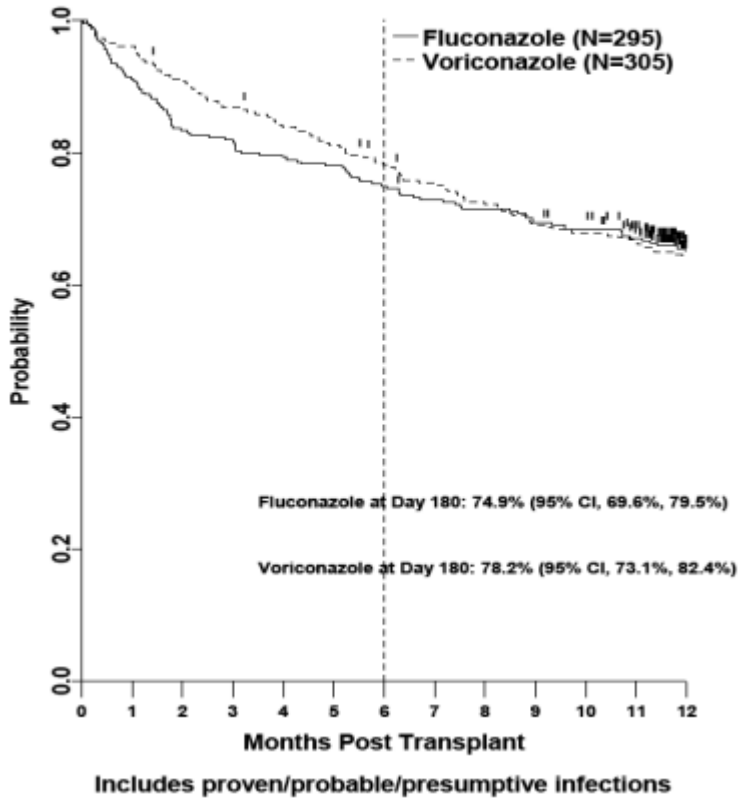
Pas d'évaluation dans la phase de neutropénie initiale

Ullmann et al. NEJM 2007

ALLOGREFFE
VORICONAZOLE: PROPHYLAXIE

Results of a Randomized, Double-Blind Trial of Fluconazole vs. Voriconazole for the Prevention of Invasive Fungal Infections in 600 Allogeneic Blood and Marrow Transplant Patients

Figure 1B



Fungal free survival

Table 2. Number of patients with invasive fungal infection (IFI) through day 365

IFI Category	Day 0-180		Day 0-365	
	FLU	VORI	FLU	VORI
Proven				
Aspergillus	3	0	5	2
Candida	3	3	3	6
Zygomycetes	1	1	2	3
Other[1]	0	1	1	3
Multiple[2]	2	0	2	1
Subtotal	*9*	*5*	*13*	*15*
Probable				
Aspergillus	14	9	16	15[5]
Other[3]	1	0	2	0
Subtotal	*15*	*9*	*18*	*15*
Presumptive	9	8	10	8
Total IFIs (Proven/Probable/Presumptive)[4]	33	22	41	38

Wingard J et al. Blood 2010

LA FLUCONAZOLE: PROPHYLAXIE

Prophylaxie des leucémies aiguës (prospectif, randomisé, double-aveugle; n=256)

Résultats	**FCZ 400**	**Pbo**	***p***
Colonisation fongique	29%	68%	< 0.001
Infections Prouvées	9%	21%	*0.02*
IF superficielles	6%	15%	0.01
IFI	4%	8%	NS
Ampho B en empirique	-	-	NS
Mortalité globale	-	-	NS

Winston DJ et al. *Ann Intern Med. 1993*

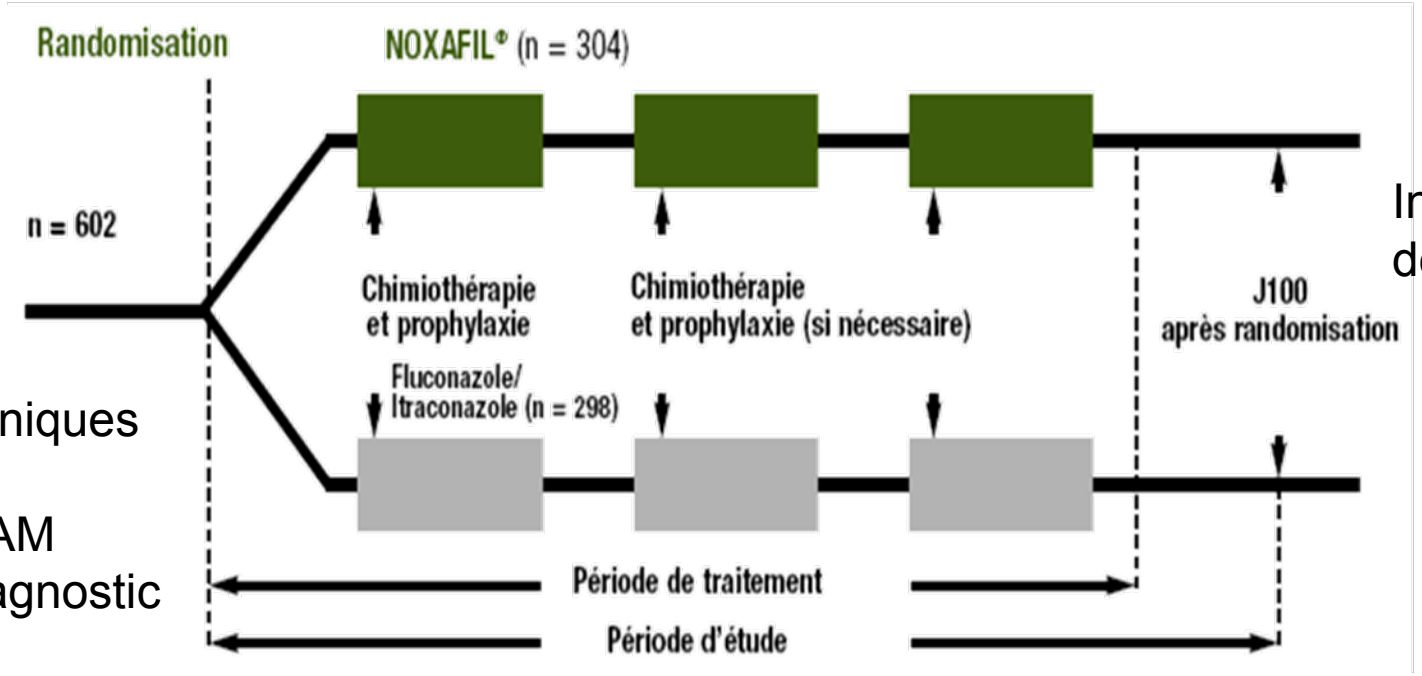
LA ITRACONAZOLE: PROPHYLAXIE

Prophylaxie chez l'adulte atteint d'hémopathies malignes avec chimiothérapie ou greffe de moelle (prospectif, randomisé, ouvert; n = 445)

Résultats	**ITRA**	**FCZ 100**	***p***
IFI prouvées	1	6	
Décès liés aux IFI prouvées	0	4	0.03
Décès d'origine fongique	0	7	0.024
Aspergilloses prouvées	0	6	0.038
Décès liés aux aspergilloses		5/6	
Recours à l'Ampho B	39	58	0.043

Morgenstern et al. *Br J Haematol. 1999*

LAM MDS
Posaconazole en prophylaxie



63% pts neutropéniques

≥ 70% LAM primo-diagnostic

Incidence des IFI ?

Cornely et al. NEJM 2007

LAM MDS
Posaconazole en prophylaxie

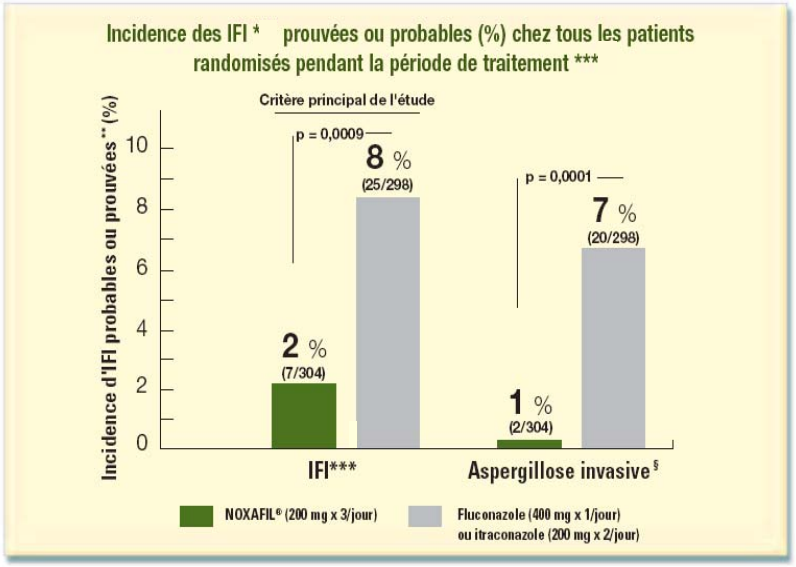
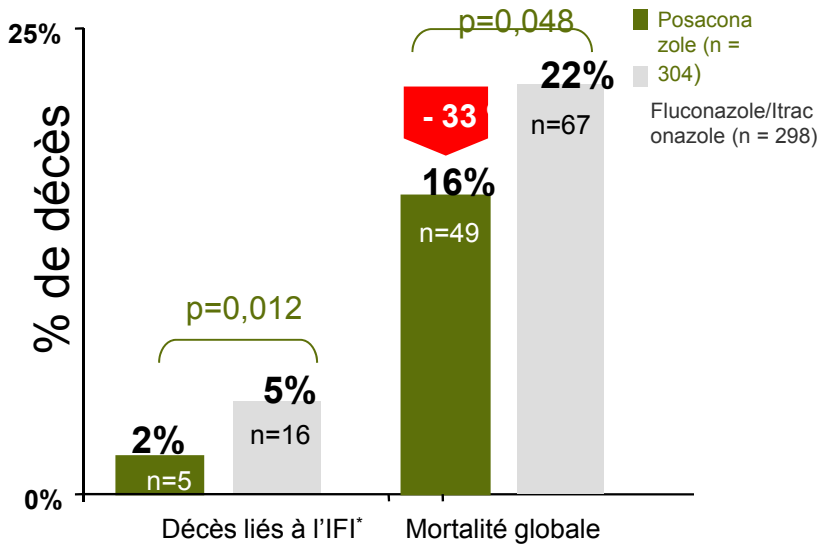


Figure adaptée des données chiffrées du RCP NOXAFIL® et du Dossier AMM NOXAFIL® (protocole P01899) p.108.
§ L'incidence de l'aspergillose prouvée ou probable n'était pas une variable pré-spécifiée pour l'analyse dans cette étude et ne fait pas partie des critères secondaires prévus[D].



Baisse significative de l'incidence des IFI et des AI *vs* fluconazole ou itraconazole

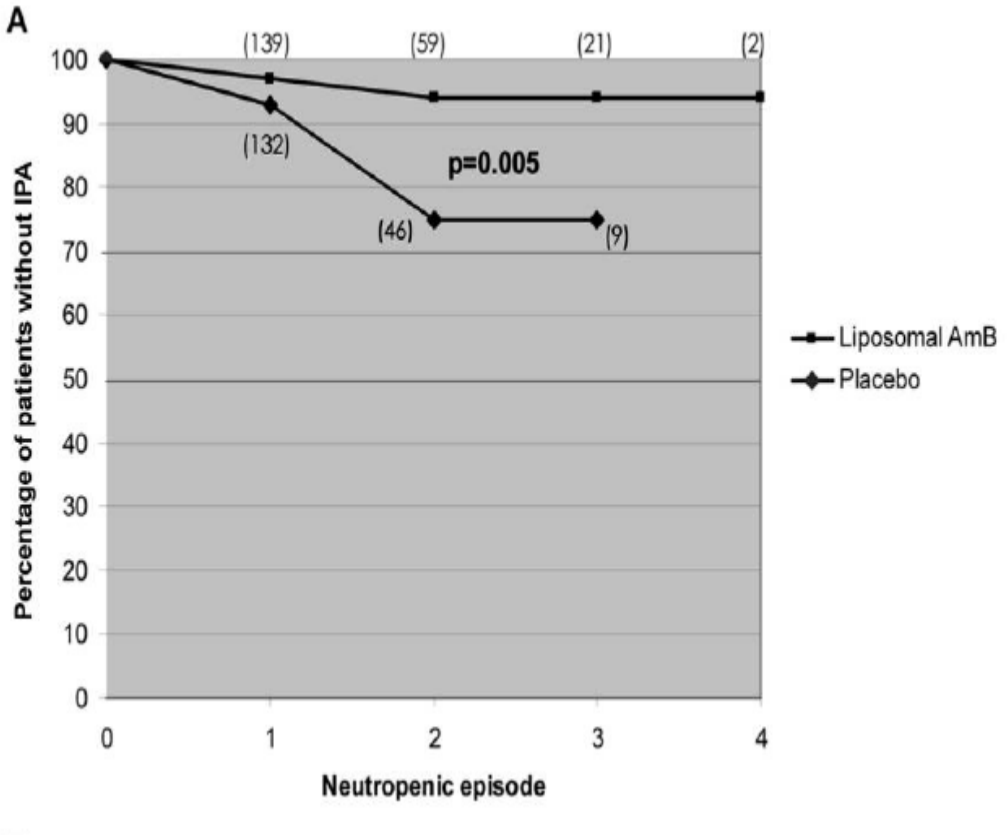
Réduction significative de la mortalité globale et liée aux IFI *vs* fluconazole ou itraconazole

Les agents pathogènes en cause retrouvés en dehors des *Aspergillus* spp étaient *Candida* spp, *Pneumocystis jirovecii*, *Pseudallescheria boydii et Rhizopus*

Cornely et al. NEJM 2007

Aérosols L AmB + fluconazole

- Hémopathie
- Prophylaxie fluco + aérosols L AmB 2X/ sem vs. Fluco + placebo
- Pas de différence de survie
- Toux ds le groups aérosols



Rijnders, CID 2008

3rd European Conference on Infections in Leukemia

Antifungal prophylaxis in leukemia patients 2009 update of the ECIL-1 and 2 guidelines

Johan Maertens (B, chair), Pascale Frère (B), Cornelia Lass-Flörl (Au), Werner Heinz (D), Oliver Cornely (D, co-chair)

September 25 - 26 2009, Juan-les-Pins - France

ELN LeukemiaNet European

Excellence in science EBMT European Group for Blood and Marrow Transplantation

EORTC European Organisation for Research and Treatment of Cancer AISBL International Non-Profit Association under Belgian law IVZW

ICHS International Society for Compromised Host

CDC Grading system (ECIL-1 and ECIL-2, Updates ECIL-3)

Quality of evidence	Strength of recommendation
I Evidence from at least one well-executed randomized trial	A Strong evidence for efficacy and substantial clinical benefit Strongly recommended
II Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments	B Strong or moderate evidence for efficacy, but only limited clinical benefit Generally recommended
III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	C Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g., drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches Optional
	D Moderate evidence against efficacy or for adverse outcome Generally not recommended
	E Strong evidence against efficacy or of adverse outcome. Never recommended

Primary antifungal prophylaxis in leukemia

- Induction chemotherapy of acute leukemia
  - **Posaconazole 200 mg tid oral: AI[2,3]**
  - Aerosolized liposomal amphotericin B in combination with oral fluconazole: BI
  - Fluconazole 50-400 mg qd iv/oral: CI[2,5]
  - Itraconazole oral solution 2.5 mg/kg bid: CI[1,2,3]
  - Polyene[4] iv: CI
  - Candins iv: insufficient data

should not be used empirically in case of prior azole prophylaxis

3. it is recommended to monitor serum drug concentrations
4. includes low doses of conventional amphotericin B and lipid formulations.
5. combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI

Primary antifungal prophylaxis in BMT

- **Allogeneic hematopoietic stem cell transplantation: neutropenic phase**
  - **Fluconazole 400 mg qd iv/oral: AI[2,5]**
  - **Voriconazole 200 mg bid oral: provisional AI**
  - Aerosolized liposomal amphotericin B plus fluconazole: BII
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole 200 mg tid oral: no data
  - Micafungin 50 mg qd iv: CI
  - Polyene[4] iv: CI
- **Allogeneic hematopoietic stem cell transplantation: GvHD phase**
  - **Posaconazole 200 mg tid oral: AI[2,3]**
  - **Voriconazole 200 mg bid oral: provisional AI**
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Fluconazole 400 mg qd iv/oral: CI[2]
  - Polyene iv: CI
  - Aerosolized liposomal amphotericin B plus fluconazole: insufficient data
  - Candins iv: insufficient data

Prophylaxie secondaire par voriconazole

- IFI prouvée ou probable (non zygo) dans les 12 derniers moi
- alloHSCT
- 45 patients (41 LA)

- Prophylaxie secondaire par voriconazole au cours allo pendant 100-150 jours
- Suivi 12 mois

Previous invasive fungal infection, n.	
Probable aspergillosis	25
Proven aspergillosis	6
Proven candidiasis	5
Other proven fungal infection	3
Filamentous infection of lung (biopsy proven, culture negative)	1
Rhodotorula mucilaginosa fungemia	1
Filamentous infection of ethmoidal sinus (biopsy proven, culture negative)	1
Other probable fungal infection	3
Pulmonary *Scedosporium* infection	1
Pulmonary infection (imaging documented)	1
Pulmonary filamentous infection	1
Previous IFI not validated by the DRC due to insufficient data or insufficient criteria*	3

Cordonnier C, Haematologica, 2010

Prophylaxie secondaire par voriconazole

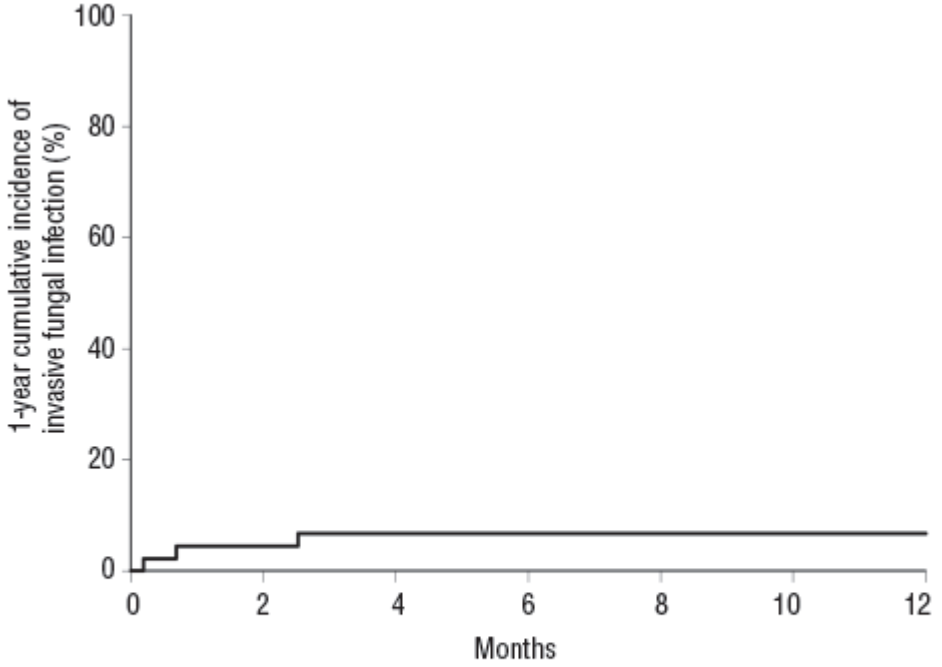


Figure 2. Cumulative incidence of invasive fungal infection (%) over the course of 12 months post-transplantation, with death as a competing risk.

Taux IFI= 3 (6,7%)
(taux attendu:30%)
1 zygo émergente
2 rechutes:
1 candidémie
1 scedosporiose
1 décès attribuable IFI
2 arrêts de traitement pour hépatotoxicité

Cordonnier C, Haematologica, 2010

PROPHYLAXIE SECONDAIRE

-166 patients, 25 centres européens, 2001-2004, IFI prouvée ou probable, pdt tt LAM (exclusion allo HSCT)
-Suivi récidive ou nouvelle IFI: 15 (27%)

Table 4. Findings during observation period, i.e. subsequent chemotherapy induced neutropenia

Characteristic, no. of patients	All patients ($n = 166$)	No or possible second IFI ($n = 140$)	Proven or probable second IFI ($n = 26$)	P value of likelihood ratio
First prophylactic regimen				
no prophylaxis given	42 (25.3%)	33 (78.6%)	9 (21.4%)	0.234
itraconazole	50 (30.1%)	43 (86%)	7 (14%)	0.699
voriconazole	24 (14.5%)	22 (91.7%)	2 (8.3%)	0.285
amphotericin B, deoxycholate	17 (10.2%)	12 (70.6%)	5 (29.4%)	0.100
amphotericin B, liposomal	10 (6.0%)	9 (90%)	1 (10%)	0.611
caspofungin	4 (2.4%)	4 (100%)	0 (0.0%)	0.383
sequential prophylaxis with different antifungals	19 (11.4%)	17 (89.5%)	2 (10.5%)	0.513

Cornely O, JAC 2008

PROPHYLAXIE SECONDAIRE

Table 5. Results of forward stepwise multiple logistic regression analysis

Variable	*P* value of Wald statistic	Odds ratio	95% Confidence interval
Factors present during observational period			
duration of neutropenia, per additional day	0.015	1.043	1.008–1.078
high-dose cytarabine	0.023	3.920	1.210–12.706
number of antibiotics, per additional antibiotic	0.014	1.504	1.089–2.086
Factors present during prior IFI			
first therapeutic antifungal is itraconazole	0.002	78.709	5.053–1226.1
HEPA	0.063	0.198	0.036–1.089
therapeutic outcome is 'partial response'	0.016	4.037	1.301–12.524
newly diagnosed AML	0.059	3.823	0.953–15.340

IFI, invasive fungal infection; HEPA, high efficiency particulate air filter; AML, acute myelogenous leukaemia.

Cornely O, JAC 2008

Secondary antifungal prophylaxis

- Condition:
  - Previously documented and fully resolved IFI plus
  - A new episode of
    - prolonged neutropenia (usually chemotherapy-induced)
    - severe immunosuppression (usually transplantation)
- Recommandation: AII
  - Cordonnier C, et al. Bone Marrow Transplant. 2004;33(9):943-8 and VOSIFI study presented at ASH 2008, San Francisco
  - Vehreschild JJ, et al. Int J Antimicrob Agents. 2009; 34(5):446-50.
  - Cornely O, et al. J Antimicrob Chemother. 2008 ;61(4):939-46.
  - Stute N, et al. Bone Marrow Transplant. 2004; 33 Suppl 1: S735
- No drug-specific recommendations possible, but choice should be based on the causative fungal pathogen of the previous IFI and the response to antifungal agents during that episode

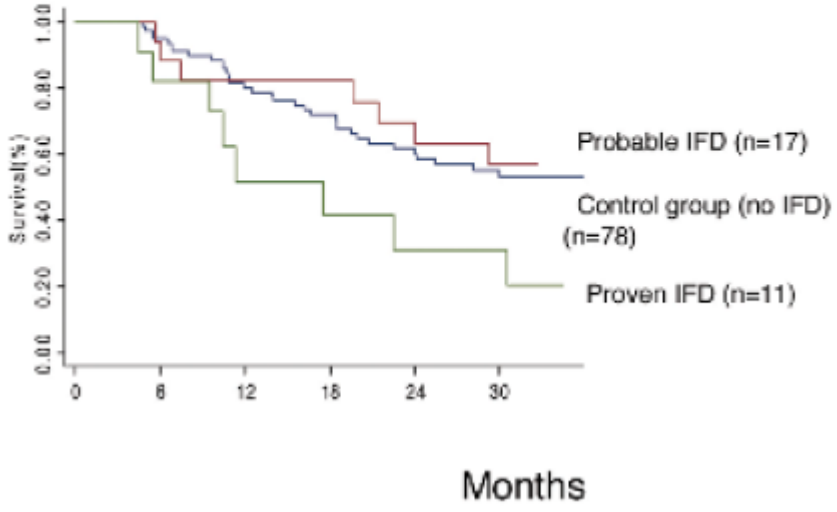
Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived to fungal disease. A case-control study

by Caroline Even, Sylvie Bastuji-Garin, Yosr Hicheri, Cecile Pautas, Francoise Botterel, Sebastien Maury, Ludovic Cabanne, Stephane Bretagne, and Catherine Cordonnier

Haematologica 2010 [Epub ahead of print]

- 28 LA, IFI prouvée ou probable, vivants à S4 vs. 78 sujets LA appariés
- Changement de chimiothérapie (retard, reduction de dose…):
  - 68% IFI
  - 24% contrôles

Figure 1B: Overall survival according to IFD



Traitement empirique

- AF patient neutropénique fébrile depuis 4-7 jours sous antibiothérapie à large spectre
- 2 études ouvertes comparant AmB d vs pas d'AF, en faveur du traitement empirique
- Difficulté d'évaluation de l'efficacité, utilisation de scores composites

Tt empirique caspofungine

- 1095 patients
- Neutropénie
- Tt empirique
  - Caspofungine
    vs.
  - L AmB
- Prophylaxie fluco: 56%

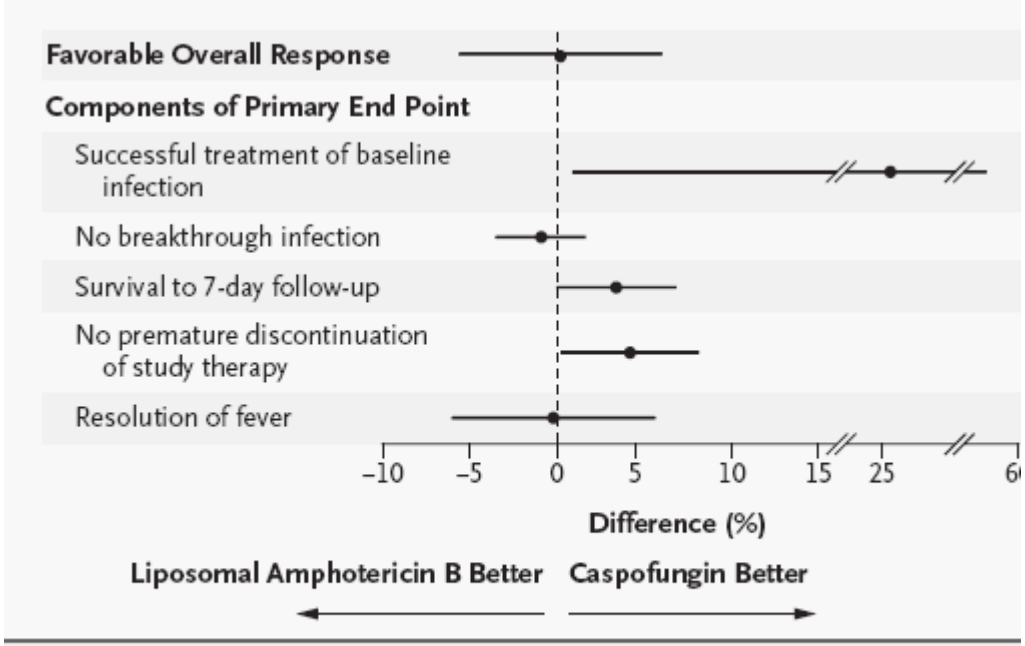


Figure 1. Differences between the Treatment Groups in the Rate of Overall Response and Components of the Primary End Point.

Walsh, NEJM, 2004

Tt empirique L AmB

- 687 patients
- L AmB vs. AmB d
- Score composite: 50% de succès dans les 2 bras
- Survenue IFI sous traitement
  - 3,2% L AmB
  - 7,8% AmB d
- Meilleure tolérance L AmB

Walsh TJ, NEJM 1999

3rd European Conference on Infections in Leukemia

Empirical Antifungal Therapy
2009 Update of ECIL-1 / ECIL-2 Guidelines

O. Marchetti, C. Cordonnier, T. Calandra

September 25 - 26 2009, Juan-les-Pins - France

ELN LeukemiaNet European

Excellence in science EBMT European Group for Blood and Marrow Transplantation

EORTC European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

ICHS International Conference on Infections in Immunocompromised Host Society

2009 UPDATE - Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

« Generally recommended. Moderate evidence »

2009 UPDATE : Antifungal Drugs for Empirical Therapy

Antifungal agent	Daily dose	CDC Grading		
		Level of Recommendation	Evidence for	
			Efficacy	Safety
Liposomal AmB	3 mg/kg	A *	I	I
Caspofungin	50 mg	A *[1]	I	I
ABLC	5 mg/kg	B [2]	I	I
Itraconazole	200 mg iv	B [1,4]	I	I
Voriconazole	2x 3 mg/kg iv	B [1,3,4]	I	I
NEW: Micafungin	100 mg	B	II	II
AmB deoxycholate	0.5-1 mg/kg	B [2] / D [5]	I	I
Fluconazole	400 mg iv	C [1,4,6]	I	I

* A double-blind, randomized trial comparing caspofungin 50 mg/m^2 (n=56) with liposomal ampho B 3 mg/kg/d (n=25) (published in abstract form) suggests a provisional grading BII
for children ; the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for 2011 update of ECIL guidelines

1 No activity against mucorales
2 Infusion-related toxicity (fever, chills, hypoxia)
3 Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis, effective therapy for candidiasis, and efficacious for prevention of breakthrough IFI.
4 Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.
5 B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosprin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).
6 No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

Failure of Empirical Therapy

- Emergence of breakthrough pulmonary zygomycosis following empirical caspofungin treatment : report of two neutropenic patients with acute leukemia and literature review

- *Hormographiella aspergillata* infections arising in neutropenic patients treated empirically with caspofungin

Traitement préemptif

- Tenir compte de la prophylaxie antifongique
- Symptomatologie clinique
- Radiologie: TDM coupes fines
- Cultures
- LBA ou biopsie si pneumopathie
- Monitoring Ag GM +/- PCR, β D glucan

1. Pas de traitement en l'absence d'éléments positifs:
↓ AEs, résistance et couts ?
2. Traitement orienté en fonction de la présentation ?

Pre-Emptive Antifungal Therapy

Objectives

- ↓ Number of patients treated with the fever-driven empirical approach:
  treat only the “true” cases, but BEFORE overt invasive fungal infection (IFI)
- ↓ Costs and toxicity

Risks of this alternative strategy compared with the empirical treatment ?

- More deaths ?
- More IFIs ?

What criteria for a pre-emptive strategy ?

- Clinical +/- radiological

Comparaison stratégies empirique et préemptive

- 2003-2006
- Neutropénie prologée, chimio ou auto
- Patients stratifiés selon prophylaxie et hémopathie
- Traitement empirique vs traitement préemptif
- AmB d ou L AmB si insuffusance rénale
- Objectif principal: survie 14 jours après la résolution de la neutropénie
- Etude de non infériorité
- Marqueurs de suivi: clinique, RP, TDM, HC, Ag GM

Cordonnier, CID, 2009

Etude Prevert

Characteristic	Empirical treatment arm (n = 150)	Preemptive treatment arm (n = 143)
Age, years		
Mean ± SD	52.0 ± 13.5	52.1 ± 14.1
Range	20–78	19–77
Female sex	64 (42.7)	58 (40.6)
Primary diagnosis		
Acute myeloid leukemia[a]	99 (66.0)	98 (68.5)
Acute lymphoblastic leukemia	8 (5.3)	3 (2.1)
Lymphoma[b]	39 (26.0)	36 (25.2)
Myeloma	4 (2.7)	6 (4.2)
Phase of therapy		
Induction therapy	70 (46.7)	67 (46.9)
Relapse treatment	8 (5.3)	6 (4.2)
Consolidation therapy	27 (18.0)	24 (16.8)
Autologous transplantation	45 (30.0)	46 (32.2)
Autologous transplantation including total body irradiation	8/45 (17.8)	6/46 (13.0)
Antifungal prophylaxis		
Any	63 (42.0)	69 (48.3)
Amphotericin orally	47 (31.3)	51 (35.7)
Fluconazole	17 (11.3)	19 (13.3)
Itraconazole	10 (6.7)	6 (4.2)

Comparaison stratégie empirique et préemptive

Table 2. Efficacy end points in the intention-to-treat population (n = 293).

Efficacy end point	Empirical treatment arm (n = 150)	Preemptive treatment arm (n = 143)	Difference (95% CI)	P[a]
Primary				
Alive at study completion	146 (97.3)	136 (95.1)	−2.2 (−5.9 to 1.4)	.31
Secondary				
IFI	4 (2.7)	13 (9.1)	−6.4 (−10.9 to −1.9)	<.02
Baseline IFI due to				
Aspergillus species	2	6	…	
Candida species	0	3	…	
Breakthrough IFI due to				
Aspergillus species	2	2	…	
Candida species	0	2	…	
IFI-related mortality	0 (0)	3 (2.1)	−2.1 (−4.1 to 0.0)	.11
Duration of temperature ≥38°C,[b] days				
Median (IQR)	13 (5–21)	12 (5–20)	…	NS
Range	1–42	1–59	…	

Après stratification:
-non infériorité non démontrée dans les chimiothérapie d'induction
-non infériorité pour les traitements de consolidation et les autogreffes

UPDATE ECIL-3 2009

Pre-Emptive Antifungal Therapy in High-Risk Neutropenic Patients

Publication	Design	Number Pts	Antifungal Agent(s)
Maertens CID 2005	Prospective, single center, no control arm	136 high-risk cohort → 19 treated	Liposomal AmB
Cordonnier CID 2009	Prospective multicenter open random. vs. EMP	150 + 143 AL + Auto-HSCT	AmB-deoxy or Liposomal AmB
Hebart BMT 2009	Prospective multicenter open random. vs. EMP	207 + 196 Allo-HSCT	Liposomal AmB
Girmenia JCO 2009	Observational, « real-life » in single center	74 persistent fever → 49 treated	Voriconazole or Liposomal AmB
Barnes JCP 2009	Observational, « real-life » in single center	125 high-risk neutropenic fever	Caspo / L-AmB / Vori
Dignan BMT 2009	Observational, « real-life » in single center	53 persistent fever → 17 treated	Caspofungin → L-AmB or Vori
Aguilar-Guisado BMT 2009	Observational, « real-life » in single center	66 persistent fever → 26 treated	4 different drugs
Riva ICAAC 2008	Observational, « real-life » in single center	143 persistent fever	AmB-deoxy or Liposomal AmB

Pre-emptive antifungal strategy is “FEASIBLE”

- Clinical + GM/CT-scan based pre-emptive: overall survival as with empirical
- Decreased use of antifungal therapy vs. empirical
- Risk of increased occurrence of IFI (*Aspergillus, Candida*) vs. empirical therapy, especially in patients with neutropenia during more than 15 days: prognostic impact of IFI ?
- Potential for early therapy of IFI in absence of fever with pre-emptive approach (missed by fever-driven empirical approach)

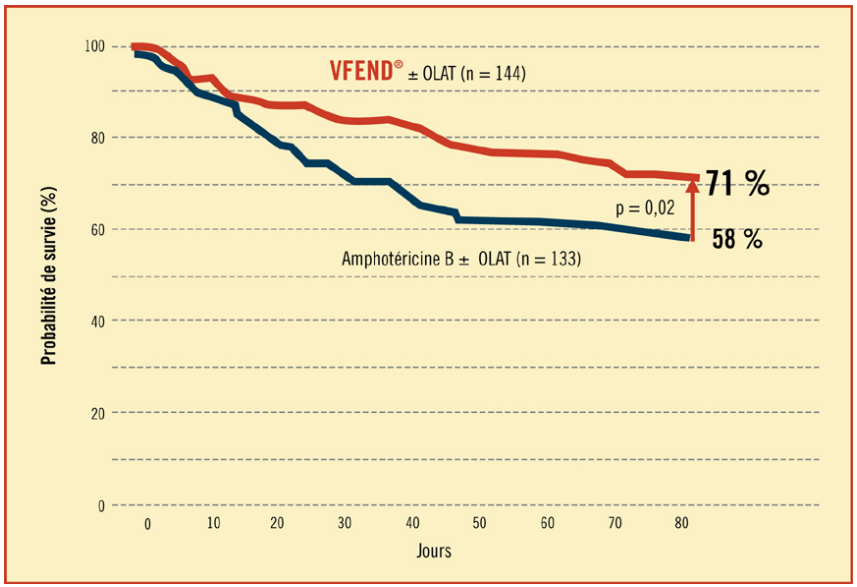
Nécessité d’évaluation avec les prophylaxies actuelles

Traitements curatifs: Aspergillose invasive

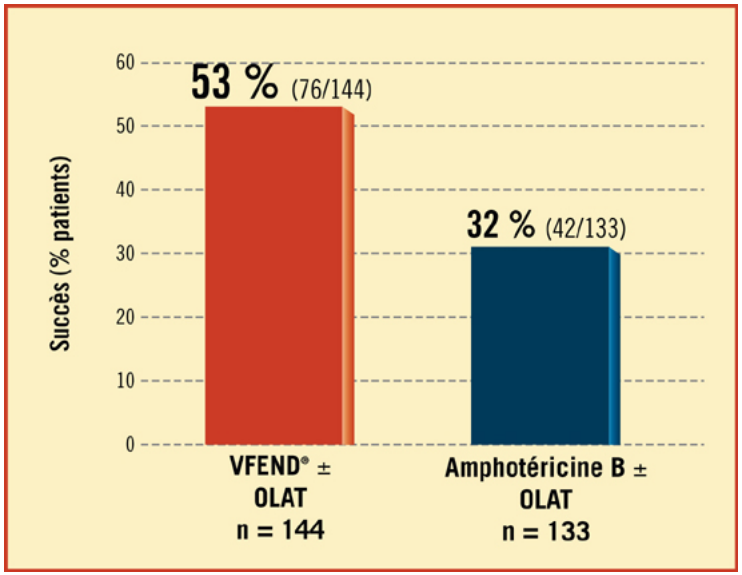
VORICONAZOLE AI

AI prouvée ou probable, 1997-2000
Voriconazole IV(n=144) 6mg/kg X 2/j J1, 4 mg X 2/j J2 vs.
Amphotericine B deoxycholate (n=133) 1-1,5 mg/kg/j
Réponses à S12

Taux de survie à la 12e semaine (MITT)



•Taux de succès global* à la 12e semaine (MITT)



Herbrecht R, NEJM, 2002

Effets indésirables les plus fréquents

Troubles visuels (45%)

Effets les plus fréquents :

- Atteinte rénale (19 dans le groupe amphotéricine B) ;
- Atteinte hépatique (7 dans le groupe VFEND)

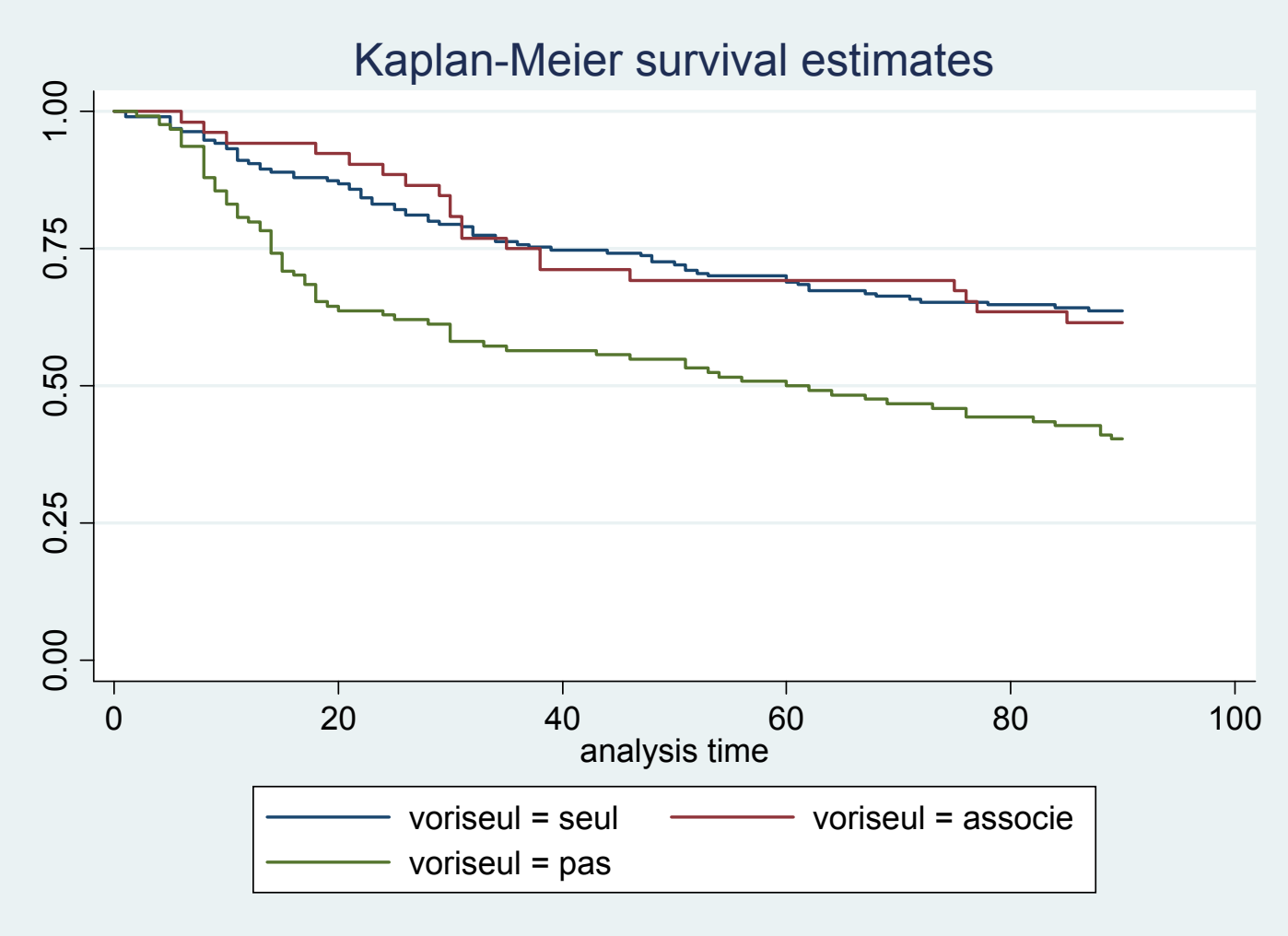
Herbrecht R et al. *N Engl J Med* 2002.

Neurotoxicité

Toxicité cutanée:

- photosensibilisation
- néoplasies cutanées

Outcome and treatment



Lortholary for SAIF. unpublished

L AmB : Tt aspergillose
Etude Ambiload

- Infections fongiques invasives prouvées ou probables (95% AI)

- AmBisome 10 mg/kg vs 3 mg/kg 2S puis 3 mg/kg

- 10 mg/kg (n=94), réponse=46%
- 3 mg/kg (n=107), réponse= 50% Néphrotoxicité et hypokaliémie plus fréquentes dans le bras 10 mg/kg

Cornely OA, CID 2007

Comparaison 2 études

	Voriconazole Herbrecht et al, NEJM	AmBisome 3 mg/kg AmBiload, Cornely et al, CID
Réponse	53% S12	50% EOT
Survie J14	91%	94%
Survie S12	71%	72%

Caspofungine: 1ere ligne aspergillose

- Hémopathie
- AI prouvée ou probable
- Caspo 1ere ligne
- 54% prophylaxe (fluco)
- 61 patients
- Objectif > 35% RP + RC

Table 2. Response to treatment at EOT in the MITT population

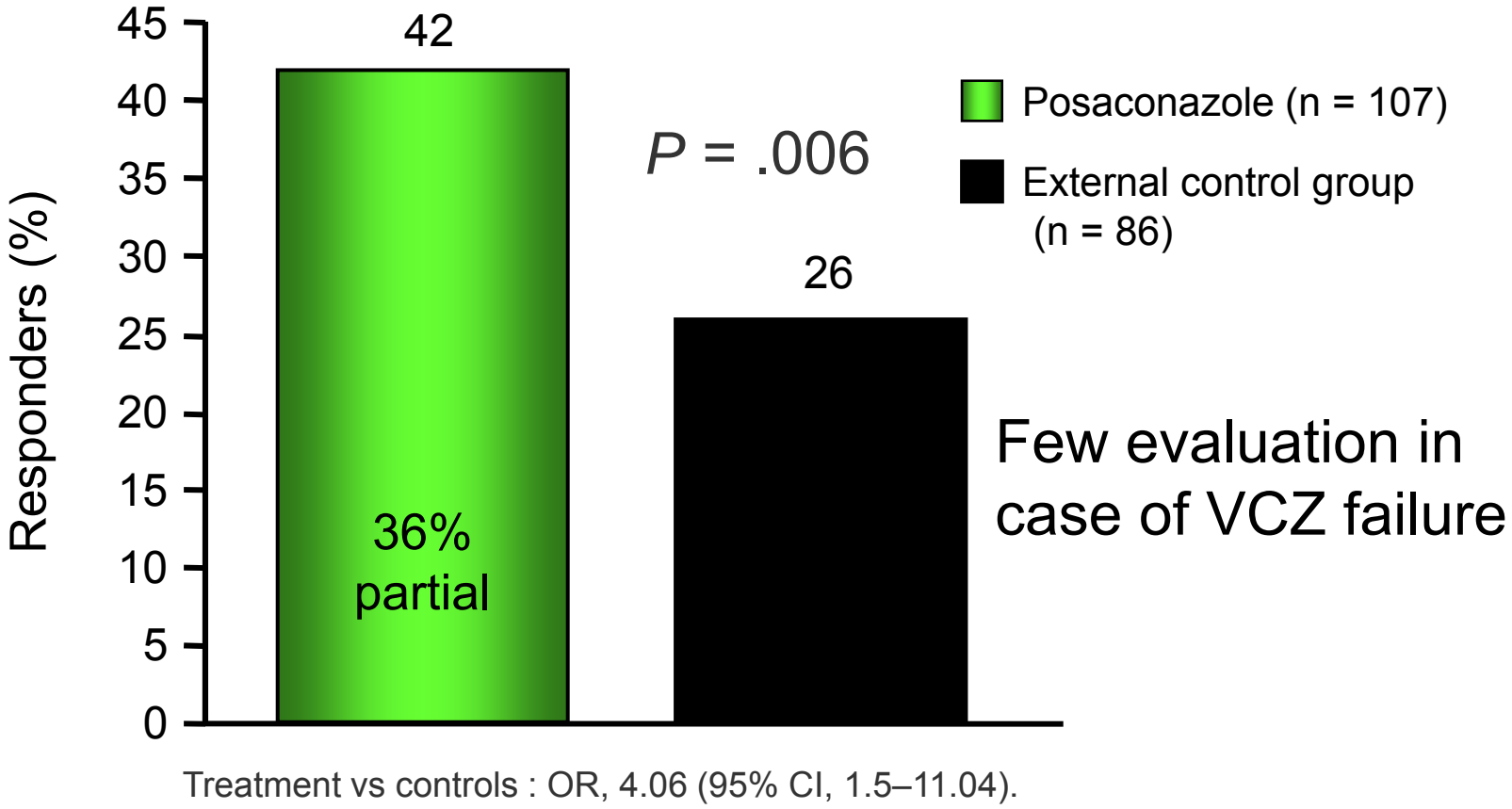
	MITT population (N=61)	
Response	n	% (95% CI)
Complete	1	2 (0–9)
Partial	19	31 (20–44)
Stable disease	9	15 (7–26)
Disease progression	31	51 (38–64)
Not evaluable[a]	1	2 (0–9)

33%

Non recommandé

Viscoli, JAC 2009

Posaconazole global response during refractory IA *



Treatment vs controls : OR, 4.06 (95% CI, 1.5–11.04).

* Principal efficacy criteria (logistic regression)

Walsh et al. CID 2007

REPONSE ET CONCENTRATION DE POSACONAZOLE

Quartile	N	Cmax (ng/ml)	Réponse
1	17	142	24%
2	17	467	53%
3	17	852	53%
4	16	1480	75%

Patients characteristics

Lebeaux et al. AAC 2009	Prophylactic treatment N=36			Curative treatment N=18			Total N=54
	<500 ng/ml	≥500 ng/ml	p	<500 ng/ml	≥500 ng/ml	p	
n (%)	16 (44)	20 (56)		4 (22)	14 (78)		
Age [mean (SD)]	44.1 (17.6)	52.5 (11.6)	0.095	31 (7.3)	44 (16.3)	0.15	48.7 (15.0)
BMI in kg/m^2 [mean (SD)]	21.6 (3.0)	24.3 (4.2)	0.055	15.8 (5.5)	22.6 (4.0)	0.07	23.2 (4.0)
Digestive disorders n (%)	10 (63)	6 (30)	0.051	3 (75)	3 (21)	0.083	22 (41)
Diarrhea n (%)	10 (63)	4 (20)	0.0093	3 (75)	1 (7)	0.018	18 (33)
Mucositis n (%)	6 (37.5)	0	0.0041	0	0		6 (11)
BMT n (%)	13 (81)	14 (70)	0.7	1 (25)	4 (28)	1	32 (59)
GVHD n (%)	12 (75)	13 (65)	0.7	1 (25)	3 (21)	1	29 (54)

ASSOCIATIONS

- Non recommandé en 1ere ligne sauf chez le transplanté rénal
  - Supériorité aux monothérapies non démontrée
  - Toxicité
  - Coût

- Si utilisé en rattrapage:
  - Caspo + Voriconazole
  - Caspo + AmphoB lipidique

UPDATE ECIL-3 2009

Invasive pulmonary aspergillosis :1st line

Agent	Grade	Comments
Voriconazole	**A I**	**2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)**
Ambisome	**B I**	**dose 3 – 5 mg/kg**
ABLC	**B II**	**dose 5 mg/kg**
Caspofungin	**C II**	
Itraconazole	**C III**	**start with iv**
ABCD	**D I**	
Amphotericin B deoxycholate	**D I**	
Combination	**D III**	

Monitorer le résiduel de voriconazole

In the absence of data in 1st line, posaconazole has not been graded

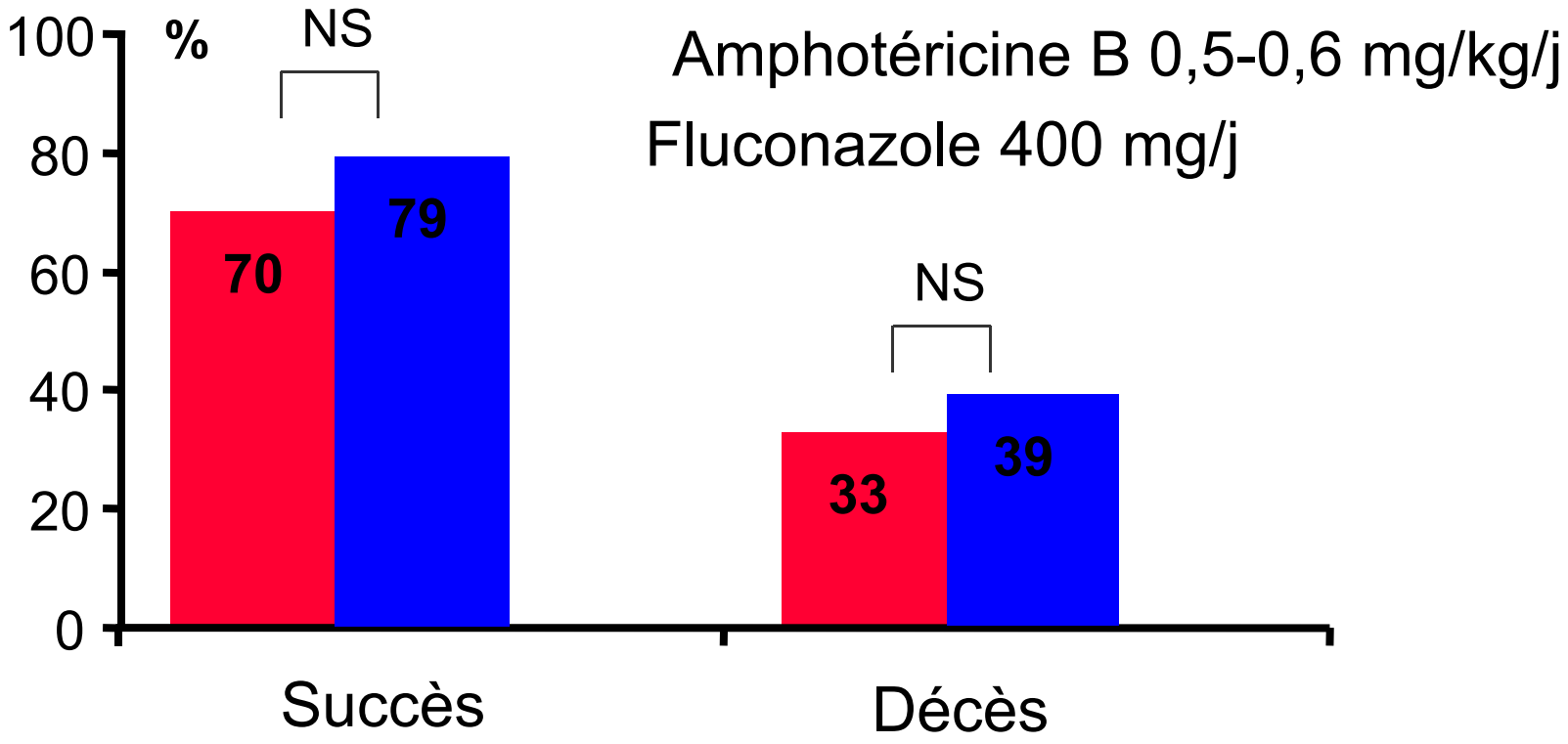
Invasive aspergillosis: salvage

Agent	Grade	Comments
Ambisome	**B III**	**no data in voriconazole failure**
ABLC	**B III**	**no data in voriconazole failure**
Caspofungin	**B II**	**no data in voriconazole failure**
Posaconazole	**B II**	**no data in voriconazole failure**
Voriconazole	**B II**	**if not used in 1st line**
Itraconazole	**C III**	**Insufficient data**

Traitement des candidoses invasives

Efficacité thérapeutique du fluconazole

Étude multicentrique : 206 candidémies chez des patients sans autre foyer infectieux documenté



Rex JH et al. NEJM 1994; 331: 1325-30.

« Résistance croisée » aux azolés chez C. glabrata (n=149)

FCZ (µg/ml) \ VRZ (µg/ml)	0.03	0.06	0.12	0.25	0.5	1	2	4	≥ 8
≤ 0.12	1								
1	1	1							
4		1	4	6	1				
8		2	15	21	16	2			
16		1	1	8	20	2			
32			1	1	8	2			1
≥64				1	3	2	3	14	10

Caspofungine in candidemia

Randomized, multicentre, double-blind trial
Non-neutropenic and neutropenic patients

Global response at end of intravenous therapy

Analysis	Caspofungin 70/50 mg n/m (%)	Amphotericin B 0,6-1.0 mg/kg n/m (%)	Estimated difference % (95.6% CI)
MITT (n=224)	80/109 (73.4)	71/115 (61.7)	12.7% * (–0,7, 26,0)
Evaluable patients (n=185)	71/88 (80.7)	63/97 (64.9)	15.4% ** (1.1, 29.7)

No difference according to species

* P = 0.09
** P = 0.03

High dose caspofungin (150 mg/d) in candidiasis

Safety outcomes

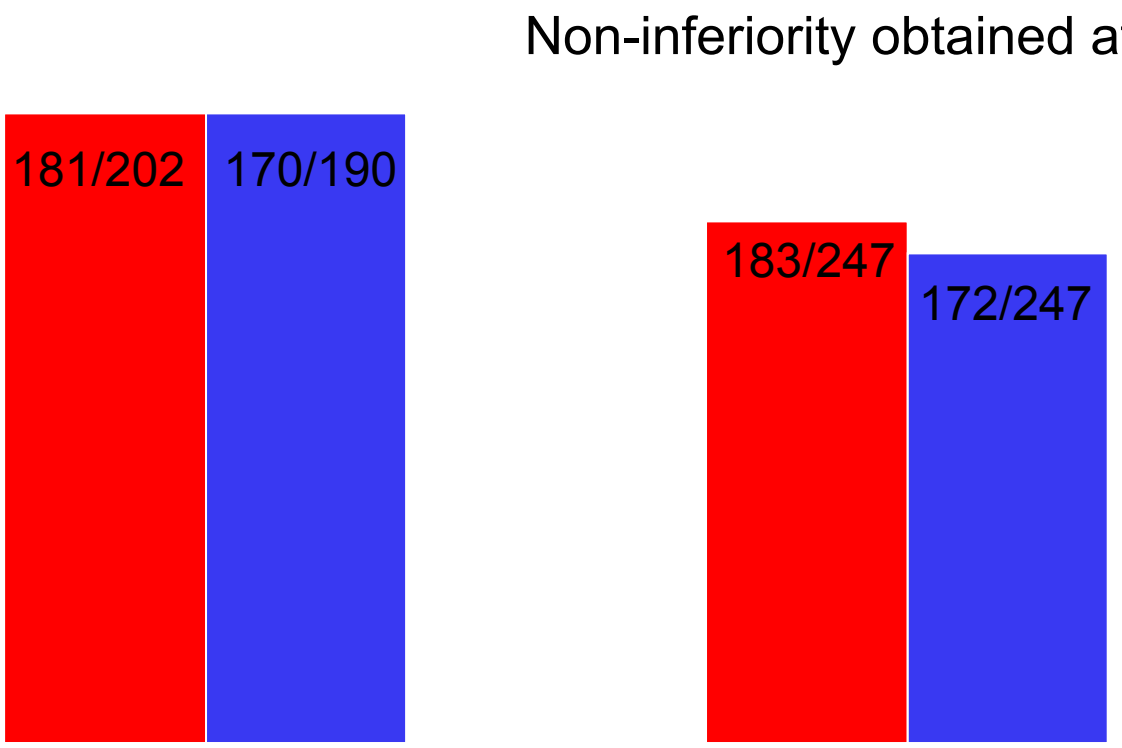
	SD (n=104)	HD (n=100)
Treat. duration	14.5 d	14.2 d
Drug related AE	20 (19%)	19 (19%)
- leading to discontin.	2 (2%)	2 (2%)

No differences in frequency and type of events

Betts et al., Clin Infect Dis, 200

Micafungin et candidémie / IC

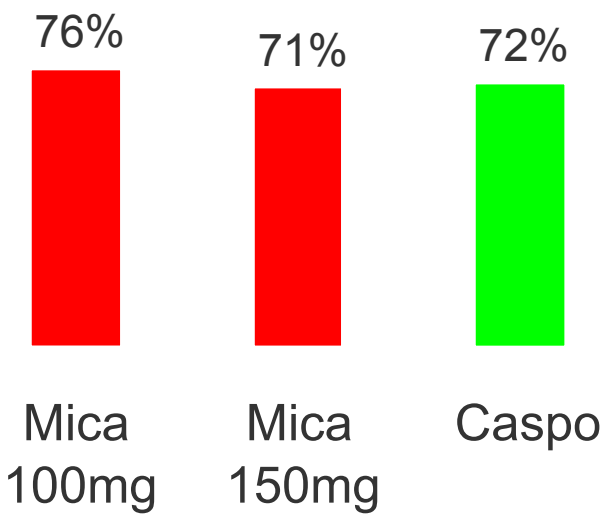
Randomized, multicentre, double-blind, non-inferiority phase III trial; non-neutropenic and neutropenic patients



Kuse et al. *Lancet* 2007.

Micafungin vs caspofungin et candidémie

- Double-blind, randomized trial in adults with candidemia or invasive candidiasis (IC) comparing:
  - micafungin 100mg/d (N=191)
  - micafungin 150mg/d (N=199)
  - std. dose caspofungin (N=188)
- Approximately 85% of patients had candidemia, 15% had IC.
- No significant differences in treatment success at EoT, mortality, relapsing/emergent infections, or AEs.



Micafungin 100mg/d and 150mg/d equivalent to standard dose caspofungin for candidemia/IC.

Pappas et al. *CID* 2007.

UPDATE ECIL-3 2009

Candidemia in hematologic patients before species identification

	Overall population	Hematological pts
Micafungin	A I	B II
Anidulafungin	A I	B II
Caspofungin	A I	B II
Ambisome	A I	B II
Other lipid-AmB	A II	B II
AmB deoxycholate		A I * C III *
Fluconazole	A I **	C III
Voriconazole	A I ***	B II

** DIII if concomitant nephrotoxic drug and EIII if renal impairment*
*** Not in severely ill patients or in patients with previous azole prophylaxis*
*** Not in patients with previous azole prophylaxis*

Candidemia: catheter removal

- Removal of central venous line
  - is a consensus recommendation for the non-hematological patients **A II**
  - in hematology patients the quality of evidence is lower **B III**
  - removal is always recommended when *C parapsilosis* is isolated **A II**

ZYGOMYCOSE: TRAITEMENT

- Terrain = correction des facteurs favorisants; diminution corticothérapie, correction du diabète
- **Exérèse chirurgicale précoce**
  - Toute localisation
  - Débridement le + complet possible parfois délabrant
  - Reconstruction après guérison
- Rôle des facteurs de croissance hématopoïétiques; transfusions leucocytaires?
- Rôle de oxygénothérapie hyperbare?

(1) Yohai RA, Surv Ophtalmo 1994; 39: 3-22. (2). Herbrecht R, Eur J Haematol Suppl 1996; 57: 12-7.

Ongoing ECIL3 recommendations for the management of zygomycosis

Management includes antifungal therapy, control of underlying conditions and surgery.

First line Antifungal therapy

Liposomal AmB

ABLC

Second line Antifungal therapy

Posaconazole

Discuss combination

A Groll, R Herbrecht, F Lanternier,O Lortholary, L Pagano, G Petrikkos, A Skiada, S Zimmerli

AMBIZYGO

Etude pilote de l'efficacité d'une posologie initiale élevée d'amphotéricine B liposomale (AmBisome®) [10mg/kg/j] dans le traitement des zygomycoses

- **Objectif principal** :
  - Evaluer à 4 semaines ou en fin de traitement si celui-ci a lieu avant 4 semaines, l'efficacité d'une monothérapie par AmBisome® à posologie élevée (10 mg/kg/j), dans le traitement initial des infections à zygomycètes. L'efficacité sera définie comme le taux de réponses objectives correspondant aux réponses complètes et partielles.
- **Critères d'inclusion**
  - **Homme ou femme, sans limite d'âge:**
  - **1) présentant** sur une **biopsie** tissulaire **des filaments larges peu septés compatibles avec un zygomycète <u>ou</u>**
  - **2) présentant un zygomycète** en culture associé à des anomalies cliniques ou radiologiques compatibles avec une infection fongique invasive évolutive dans les 72 heures précédant l'inclusion et ce quelle que soit la pathologie sous-jacente du patient

Fusariose

- Réséquer les tissus infectés
  (sinus, œil, peau, os …)
- Retrait d'un cathéter infecté
- Voriconazole = 1ere ligne, 9/21 : 44% réponse favorable; survie à 3 mois = 71%
- Ampho B
  - Fungizone: 1 – 1,5 mg/kg/j (≥ 70% échec en hémato)
  - Complexe lipidique: ≥ 5 mg/kg/j [46% efficacité]
- Posaconazole = 21 patients réfractaire/intolérance
  - Succès chez 10/21 (48%); 67% si récupération hématologique; 20% si neutropénie persistante
- (transfusions de granulocytes)

Kontoyiannis Leuk Lymphoma 2004; Perfect CID 2005; Perfect CID 2003; Raad CID 2006

Fusariose : Voriconazole

- Etude rétrospective internationale à partir de 2 bases de données: 73 pts avec infection prouvée (n=67) ou probable (n=6) tous traités par voriconazole (++2e ligne).
- Allogreffe CSP (18%), hémopathie maligne (60%), immunosuppression chronique (12%)
- Cerveau (5%), disséminée non cérébr (67%), poumons/sinus (15%), autres (12%). Neutropéniques = 64%.
- Succès = 47%, significativement influencé par neutropénie
  - Allogreffe CSP = 38%; hémato 45%; IC 44%; autre 71%
  - Cerveau 0%; disséminée 45%; autre 56%; sinus/poumons 64%
- Survie à J90 = 42%

Lortholary et al. AAC 2010

- Prophylaxie à définir en fonction du risque du patient
- Attitude préemptive ou empirique à définir en fonction des possibilités diagnostiques et environnement (HEPA)
- Mesurer bénéfice risque schéma chimiothérapie