

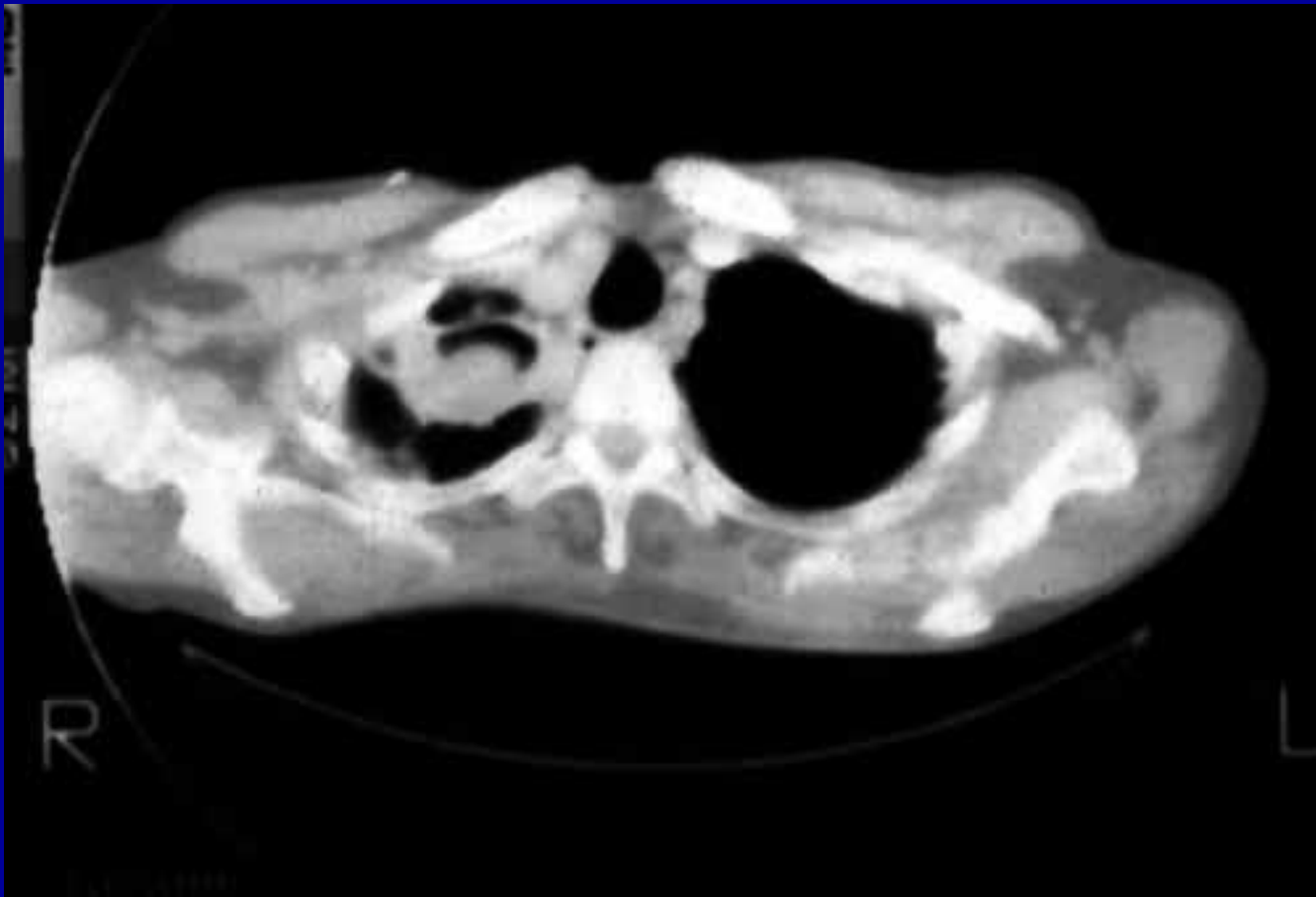
Prise en charge anti fongique des patients neutropéniques

N Milpied
Hématologie
CHU Bordeaux

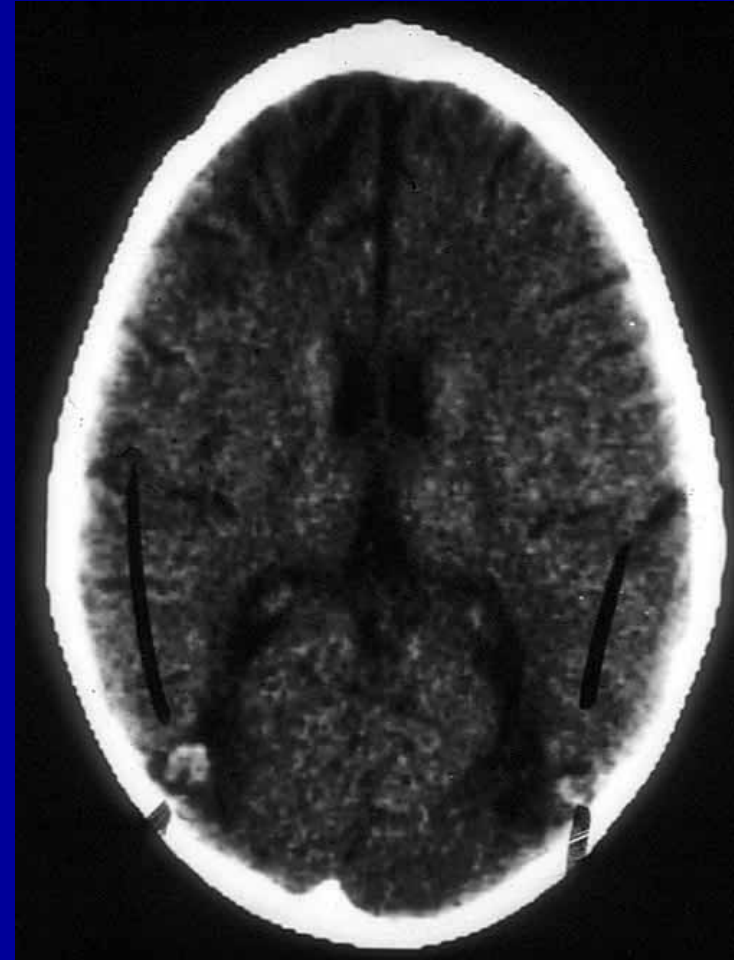
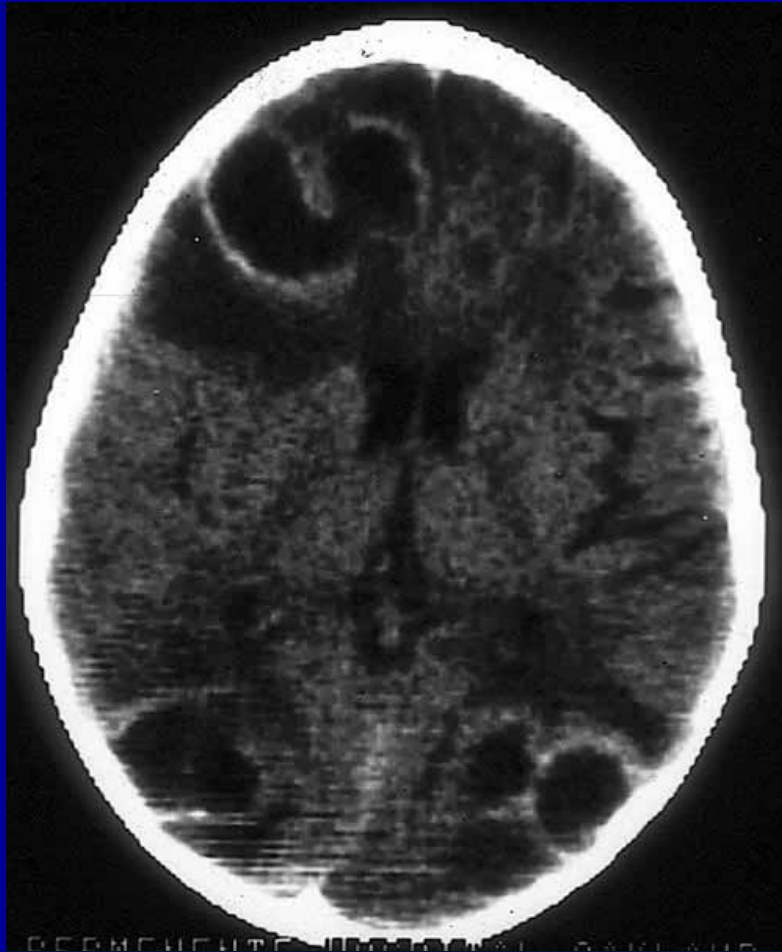
Alger mai 2007

Les risques d'infection fongique en hématologie

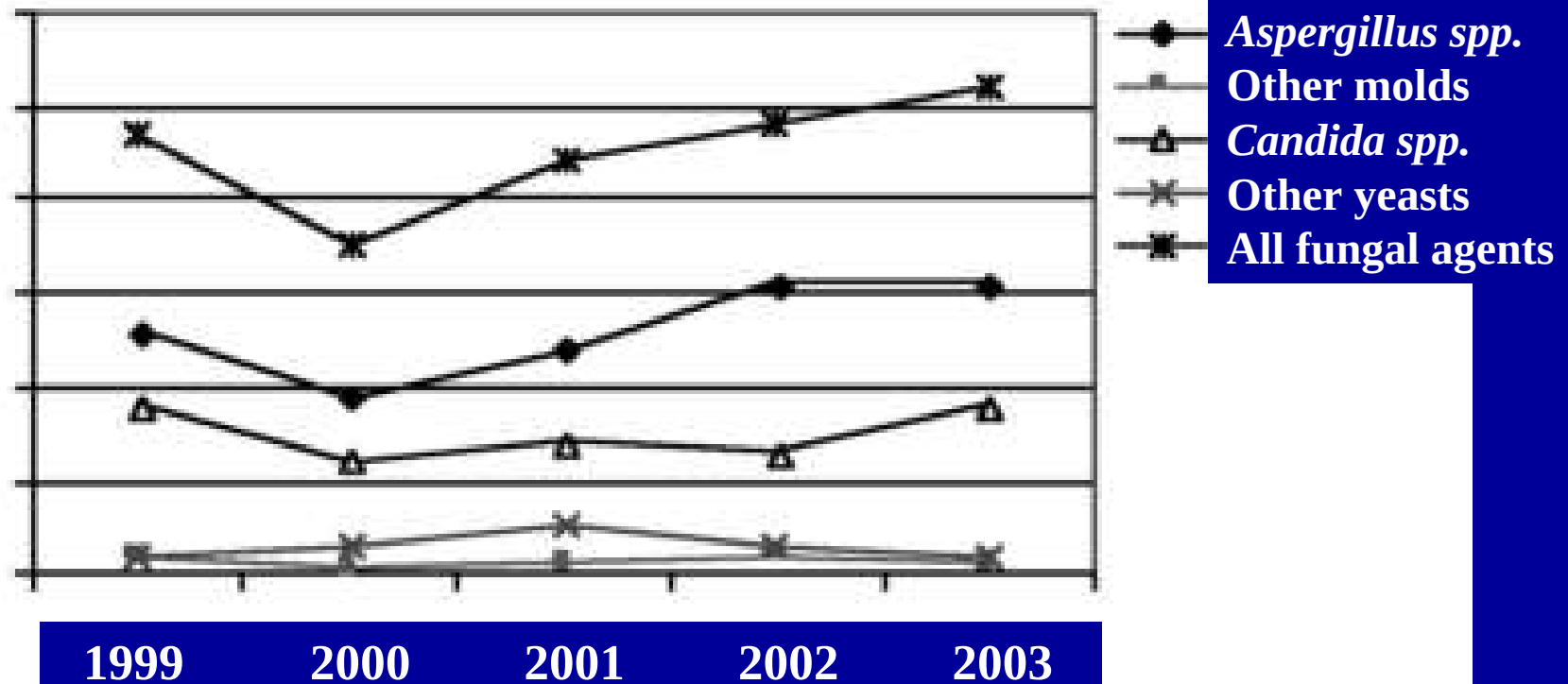
Aspergillose pulmonaire: croissant gazeux



Aspergillose cérébrale



The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study



Annual incidence rates for IFI

RR 1.1 (95% CI 0.86-1.42; $p=0.452$)

Livio Pagano et al

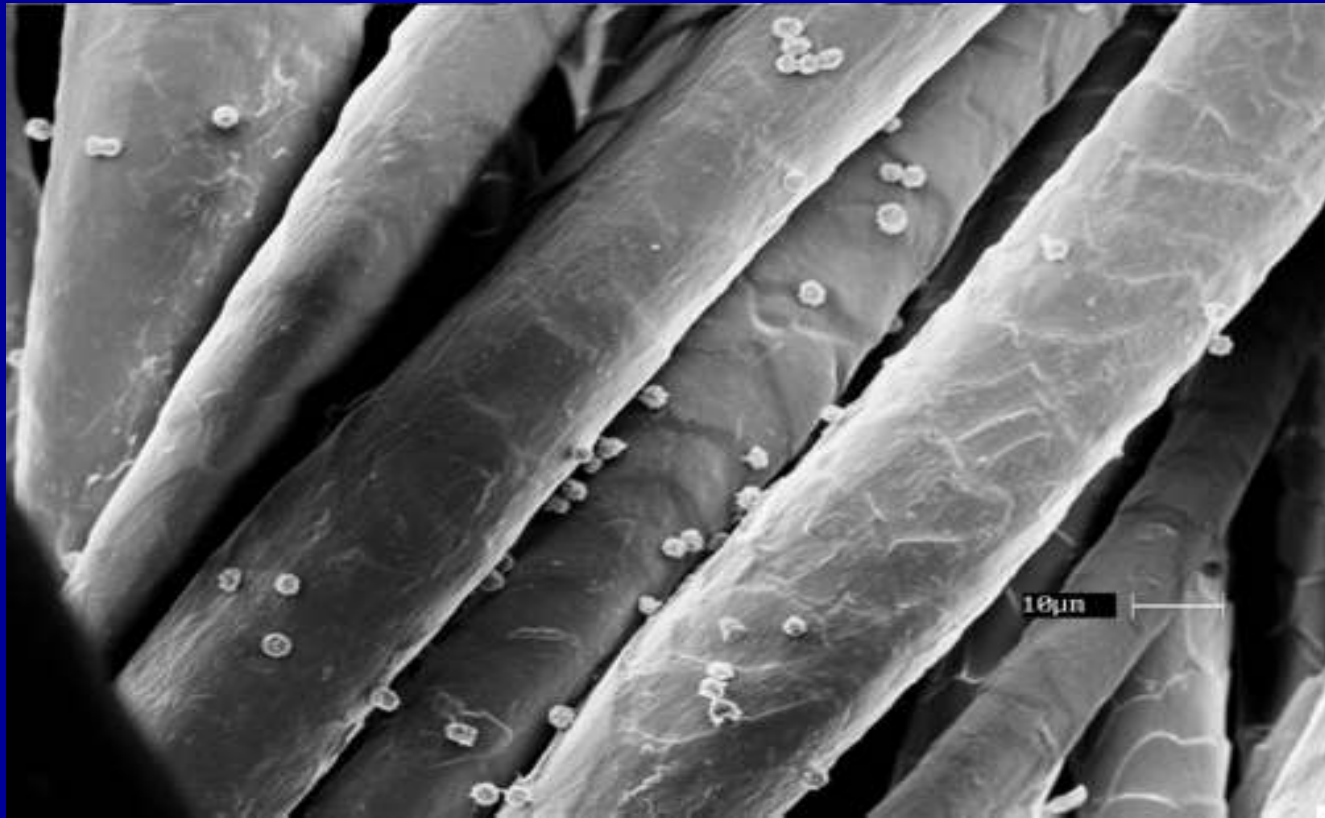
haematologica/the hematology journal : 2006; 91(8) : 1069

Table 1. Incidence of mold and yeast infections in patients with different types of hematologic malignancies.

<i>HM</i>	<i>No. of patients</i>	<i>No. of IFI (incidence)</i>	<i>Molds</i>		<i>Yeasts</i>	
			<i>No. cases</i>	<i>Incidence %</i>	<i>No. cases</i>	<i>Incidence %</i>
AML	3012	373 (12%)	239	7.9	134	4.4
ALL	1173	77 (6.5%)	51	4.3	26	2.2
CML	596	15 (2.5%)	14	2.3	1	0.2
CLL	1104	6 (0.5%)	5	0.4	1	0.1
NHL	3457	54 (1.6%)	30	0.9	24	0.7
HD	844	6 (0.7%)	3	0.35	3	0.35
MM	1616	7 (0.5%)	4	0.3	3	0.2
Total	11802	538 (4.6%)	346	2.9	192	1.6

Livio Pagano et al
haematologica/the hematology journal : 2006; 91(8) : 1069

Spores aspergillaires sur un pull

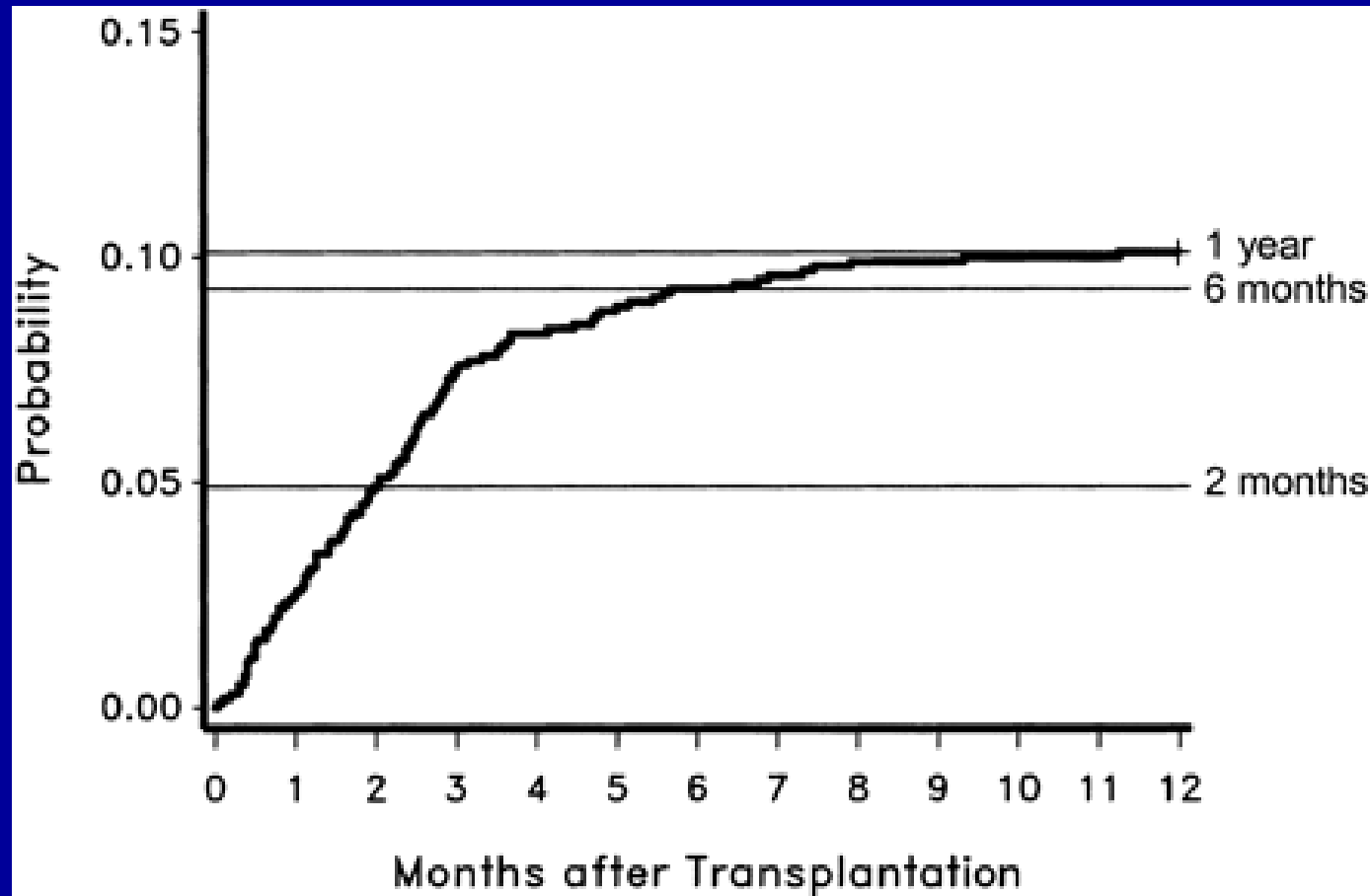


Infections à levures et champignons filamenteux lors de différentes hémopathies malignes.

N° Pts 11802	Cas	Décès (AMR%)	Mortalité (%)	Cas	Décès (AMR%)	Mortalité (%)	Cas	Décès (AMR %)	Mortalité (%)
Filament		Aspergillus			Zygo			Fusarium	
	310	129 (42)	1,1	14	9 (64)	0.07	15	8 (53)	0.07
Levures		Candida sp			Crypto			trichosp	
	175	57 (33)	0.5	8	4 (50)	0.04	7	2 (29)	0.02

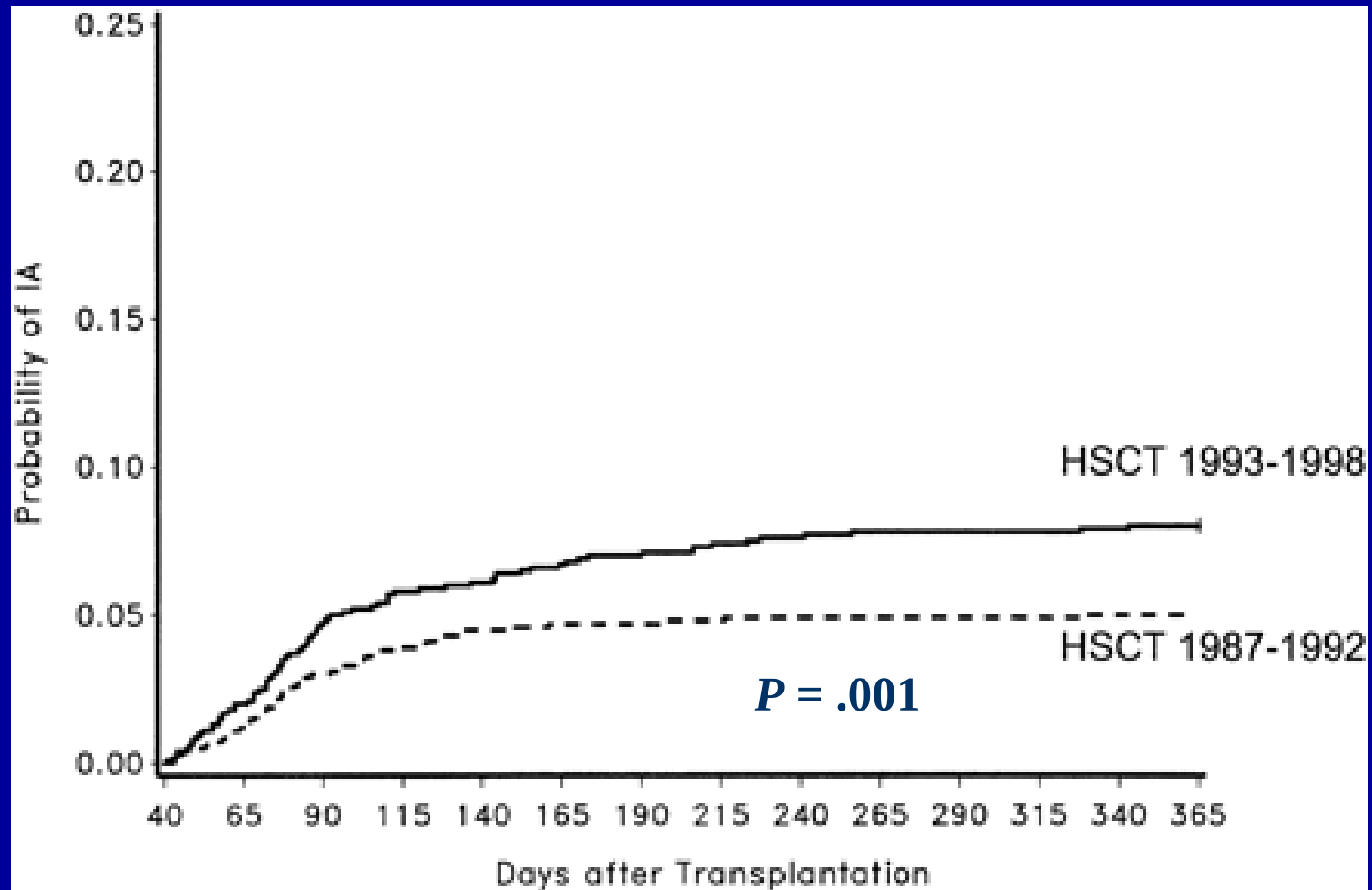
Livio Pagano et al
haematologica: 2006; 91(8) : 1069

Probability of developing proven or probable IA after HCT



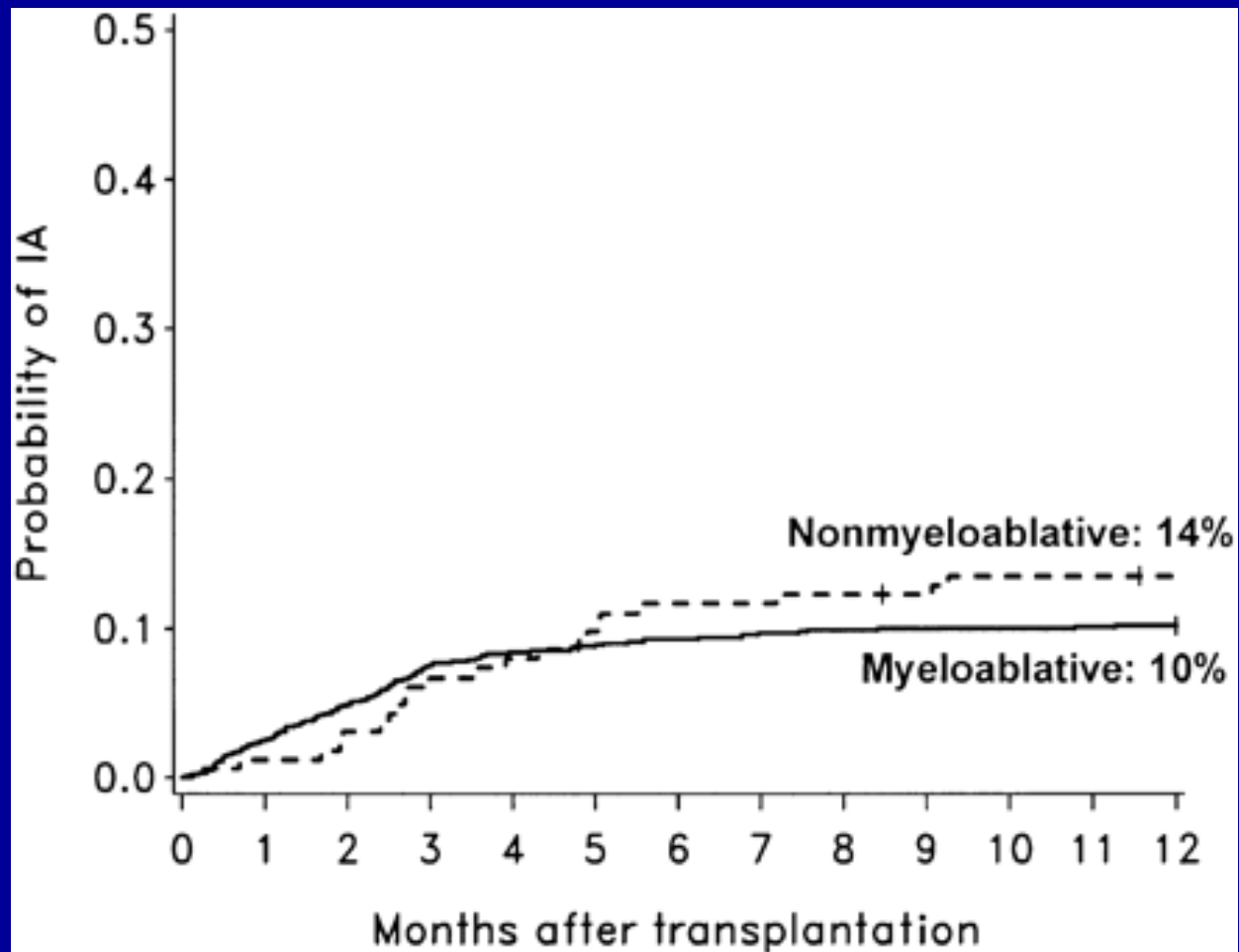
Kieren A. Marr et al Blood: 2002; 100: 4358

Probability of developing proven or probable IA among patients alive at day 40 in 2 cohorts $\geq$ / $<$ 1992



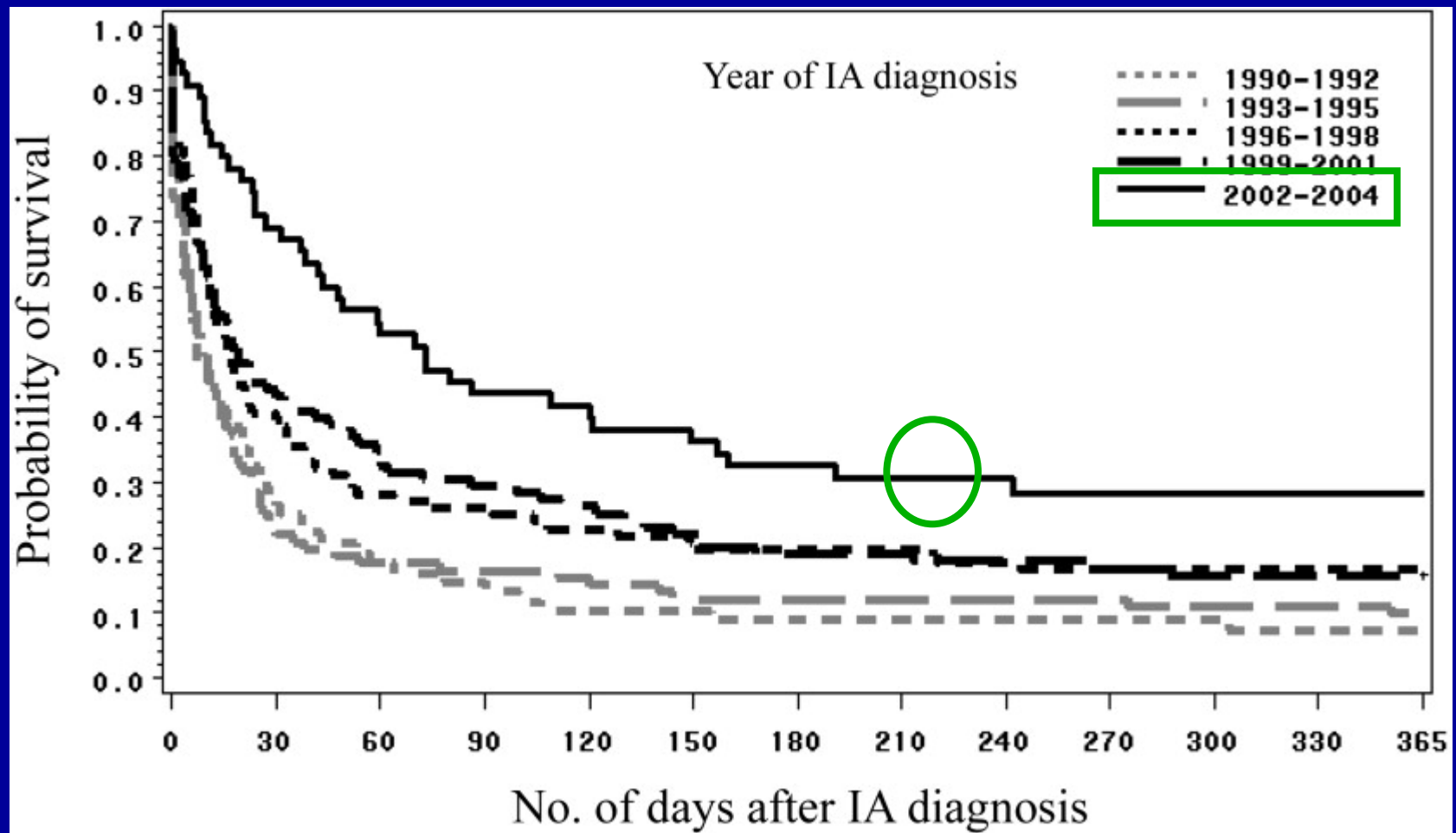
Kieren A. Marr et al Blood: 2002; 100: 4358

Invasive aspergillosis after nonmyeloablative and myeloablative HCT.

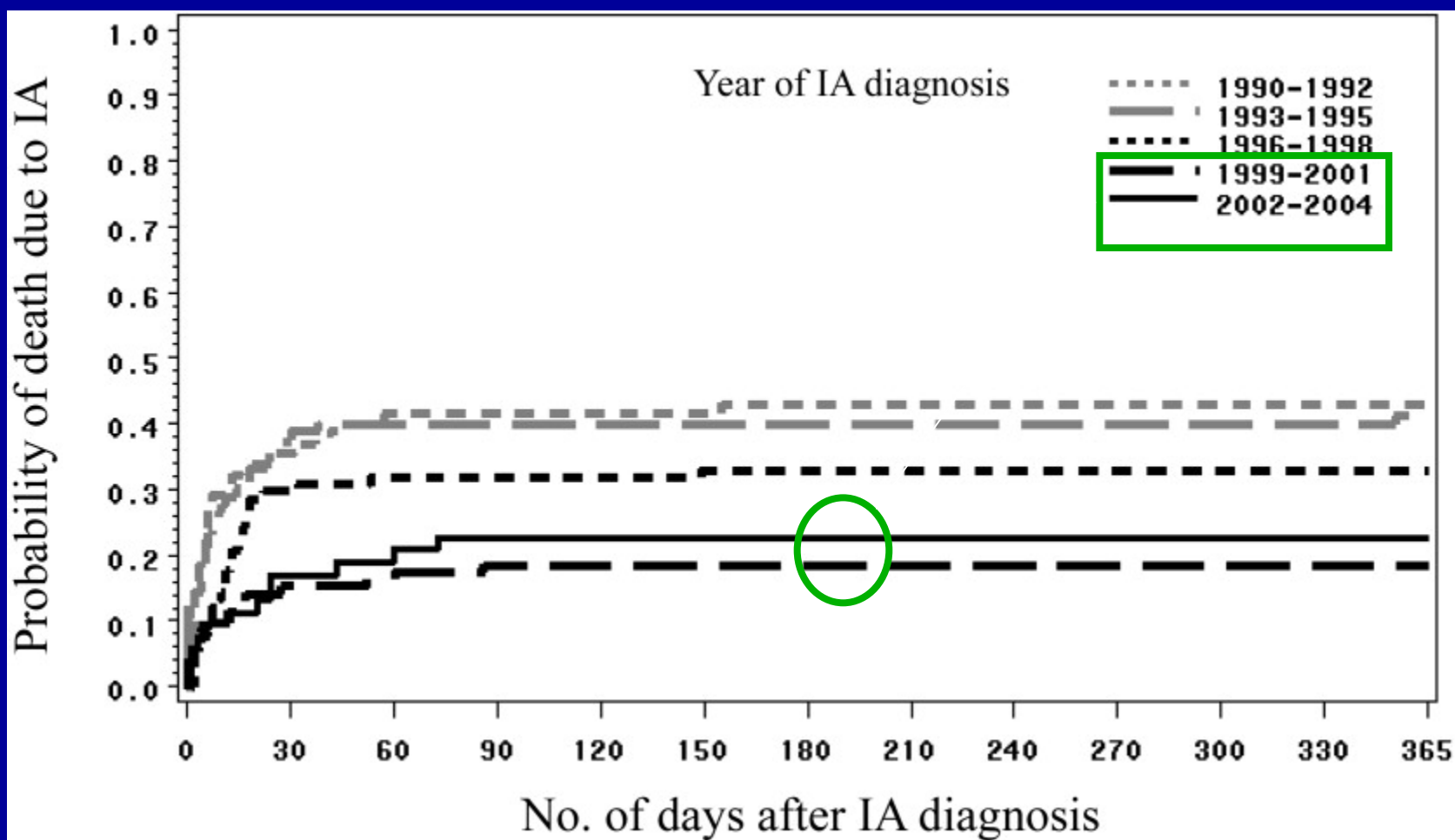


Takahiro Fukuda et al Blood 2003; 102: 827-833

Aspergillose invasive après greffe de cellules souches hématopoïétiques: Survie et facteurs pronostiques



Aspergillose invasive après greffe de cellules souches hématopoïétiques: Survie et facteurs pronostiques



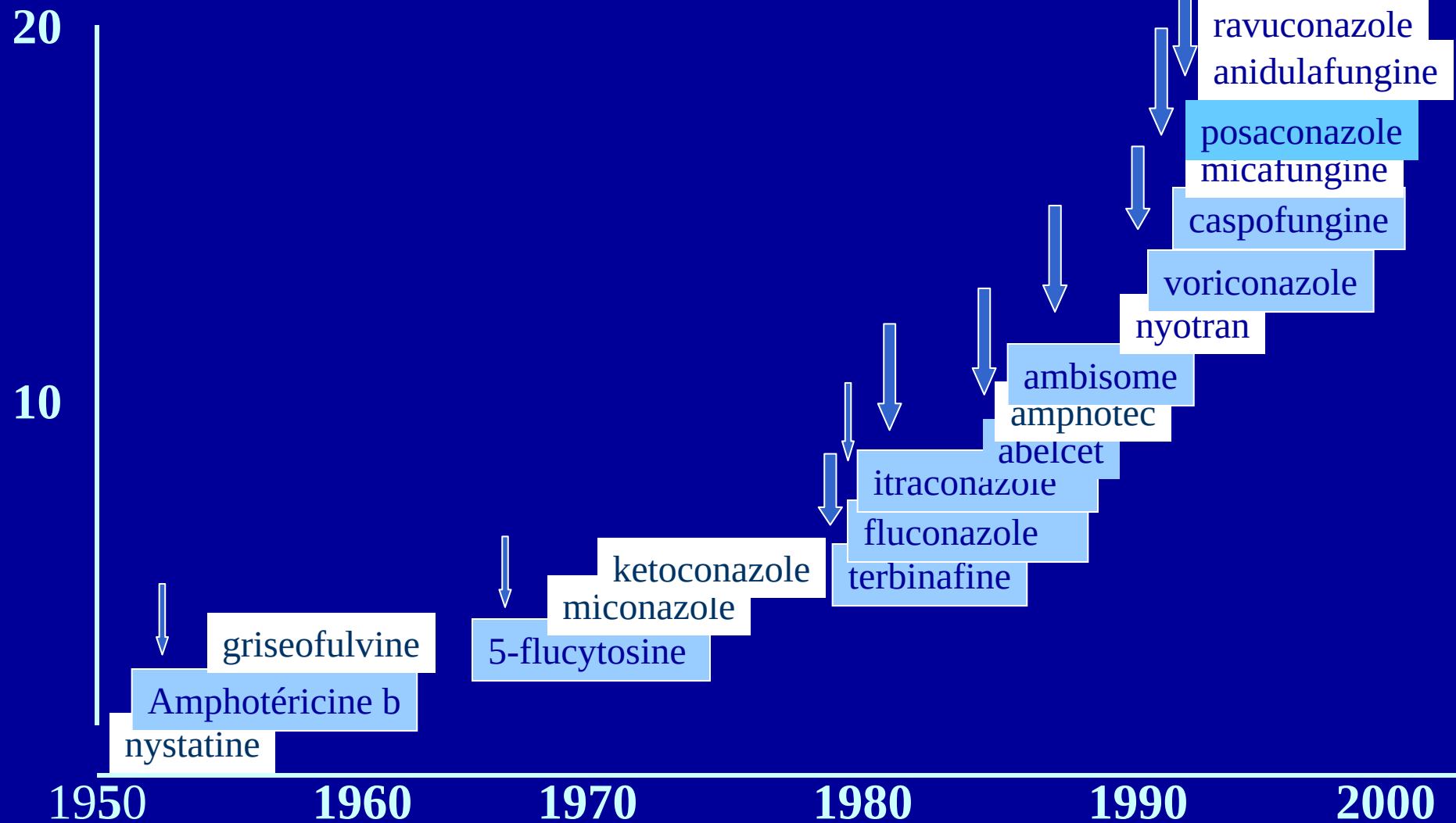
Facteurs de risque de décès chez 405 receveurs de greffe de CSH avec une aspergillose invasive

	Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P
Recipient-related factors				
Year of IA diagnosis (2002–2004 vs. previous)	0.6 (0.5–0.9)	.008	...	...
Good-risk underlying disease	0.7 (0.5–0.9)	.001	NS	NS
Severe impairment on PFT	1.6 (1.0–2.8)	.07	2.0 (1.1–3.8)	.03
Transplant-related factors				
HLA mismatch	1.3 (1.0–1.6)	.04	1.4 (1.1–1.8)	.02
Unrelated donor	1.3 (1.1–1.6)	.008	NS	NS
Receipt of PBSCs	0.7 (0.6–0.9)	.009	0.8 (0.6–1.0)	.08
Nonmyeloablative conditioning	0.6 (0.4–0.9)	.006	0.6 (0.4–1.0)	.05

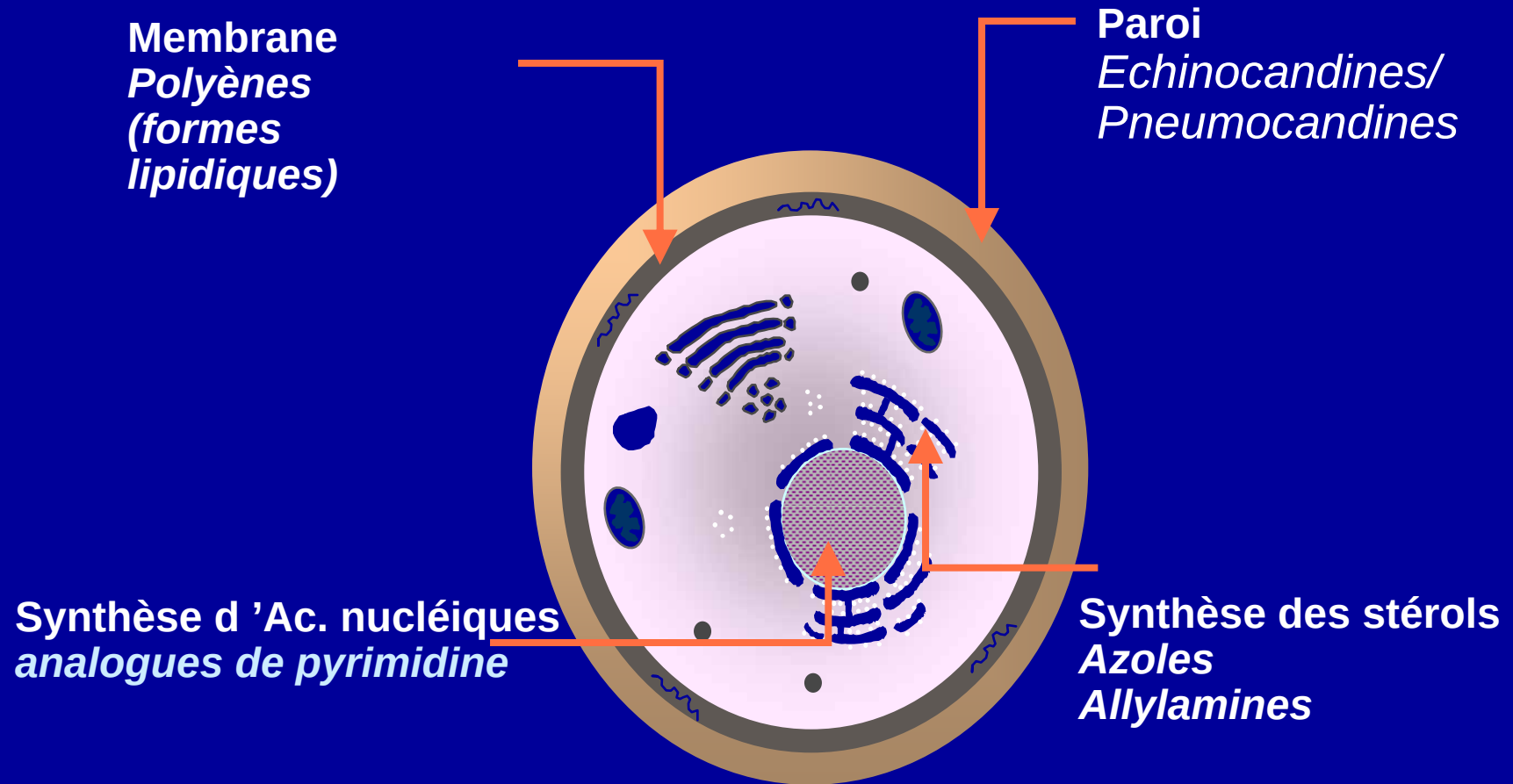
Arlo Upton et al. Clinical Infectious Diseases 2007;44:531-540

Les médicaments antifongiques disponibles

Molécules antifongiques disponibles ou en développement



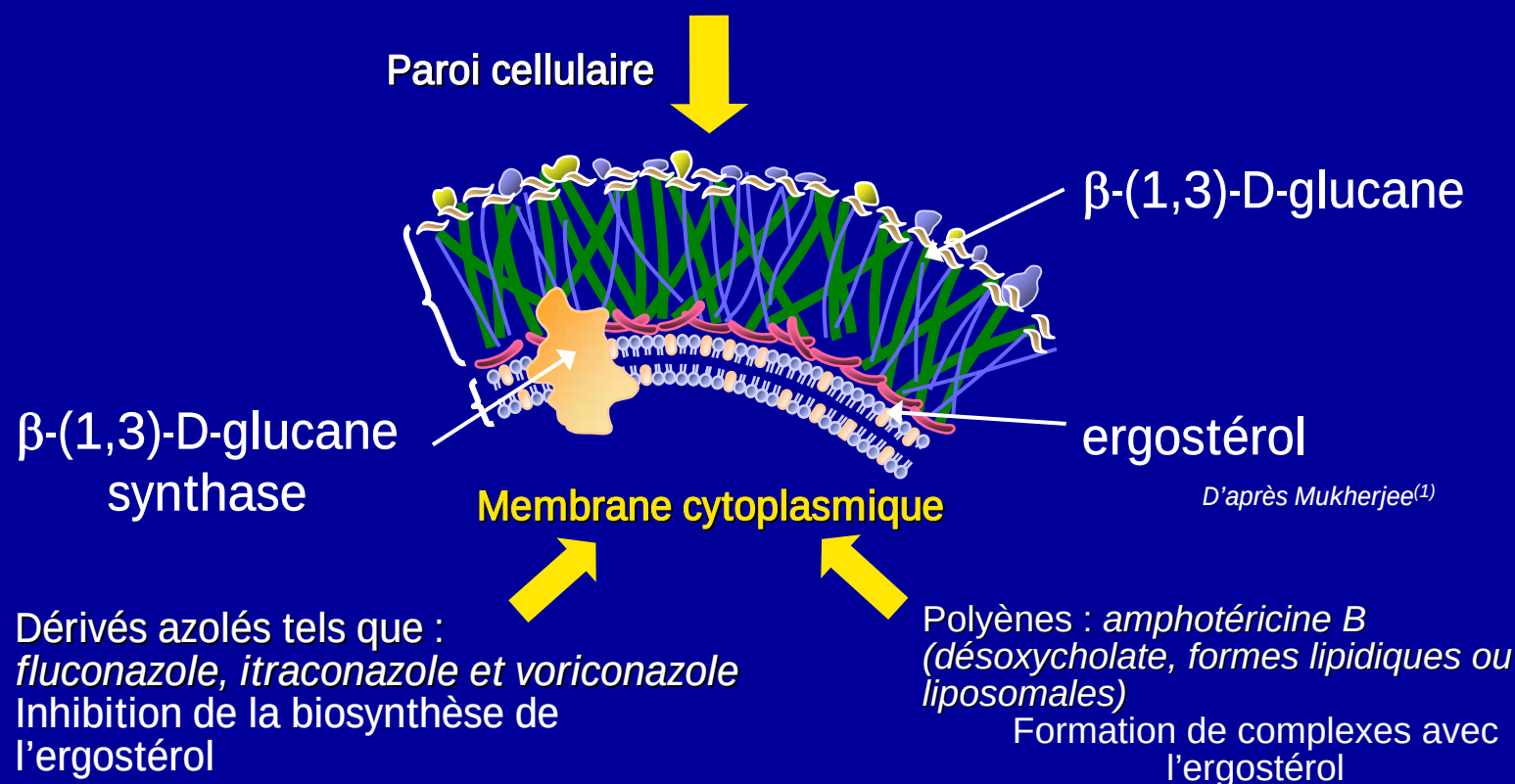
Principaux antifongiques



Un mécanisme d'action ciblé et différent des autres antifongiques systémiques

Echinocandine : *caspofungine*

Inhibition de la synthèse du $\beta(1,3)$ -D-glucane* qui rompt l'intégrité de la paroi cellulaire fongique aboutissant à la lyse



Autre action sur le noyau : *5-flucytosine* Inhibition de la synthèse protéique et de l'ADN

* Ce composant n'est pas présent dans les cellules de mammifères

(1) Mukherjee PK. et al. Combination treatment of invasive fungal infections. *Clinical Microbiology Reviews*, Jan. 2005, p163-194.

Spectre d'activité des antifongiques

	FUNGIZONE®	ANCOTIL®	TRIFLUCAN®	SPORANOX®	VFEND®	CANCIDAS®
<i>Candida</i> sp.						
<i>C. albicans</i>	S	S/R	S	S	S	S
<i>C. glabrata</i>	S/I	S	SDD/R	SDD/R	S/??	S
<i>C. parapsilosis</i>	S	S	S	S	S	S/??
<i>C. tropicalis</i>	S	S	S/SDD	S	S	S
<i>C. krusei</i>	S/I	I/R	R	SDD/R	S/R	S
<i>C. lusitaniae</i>	S/R	S	S	S	S	S
<i>Aspergillus</i> sp.						
<i>A. fumigatus</i>	S	R	R	S	S	S
<i>A. flavus</i>	S	R	R	S	S	S
<i>A. terreus</i>	S	R	R	S	S	S

S : Sensible

SDD : Sensibilité dose-dépendante

I : Intermédiaire

R : Résistant

Conférence de Consensus 2004. Prise en charge des candidoses et aspergilloses invasives de l'adulte. SFAR, SPILF, SRLF.

Spectre des antifongiques

Champignon	AmphoB	FCZ	ITZ	Voriconazole	Caspofungin
<i>C. albicans</i>					
<i>C. glabrata</i>					
<i>C. krusei</i>					
<i>Aspergillus</i> spp.					
<i>Fusarium</i> spp.					
<i>Mucor</i> spp.					
<i>Cryptococcus</i> spp.					
<i>P. carinii</i>					

Caspofungine : activité *in vitro*

- La caspofungine reste active sur les souches de *Candida* présentant une résistance intrinsèque ou acquise à l'égard du fluconazole, de l'amB ou de la flucytosine*

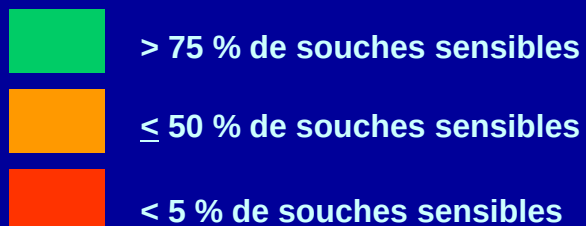
	CMI (g/ml)		CMF (g/ml)	
	MK-0991	AmB	MK-0991	AmB
<i>Candida albicans</i> : Résistant à 5FC, FCZ, KTZ, AmB (N=9)	0,125 à 1	0,50 à 4	0,06 à 0,25	0,5 à 8
<i>Candida tropicalis</i> : Résistant à FCZ (N=1)	0,125	1	0,25	1
<i>Candida glabrata</i> : Résistant à 5FC (N=2)	0,50	0,50 à 1	0,25 à 0,50	0,50 à 1
<i>Candida lusitanae</i> : Résistant à AmB (N=2)	1-2	8	1	8

Induction de résistance** : Après 40 passages successifs de *Candida* exposé à des concentrations subinhibitrices de caspofungine, aucune modification significative de la CMI ni de la CMF

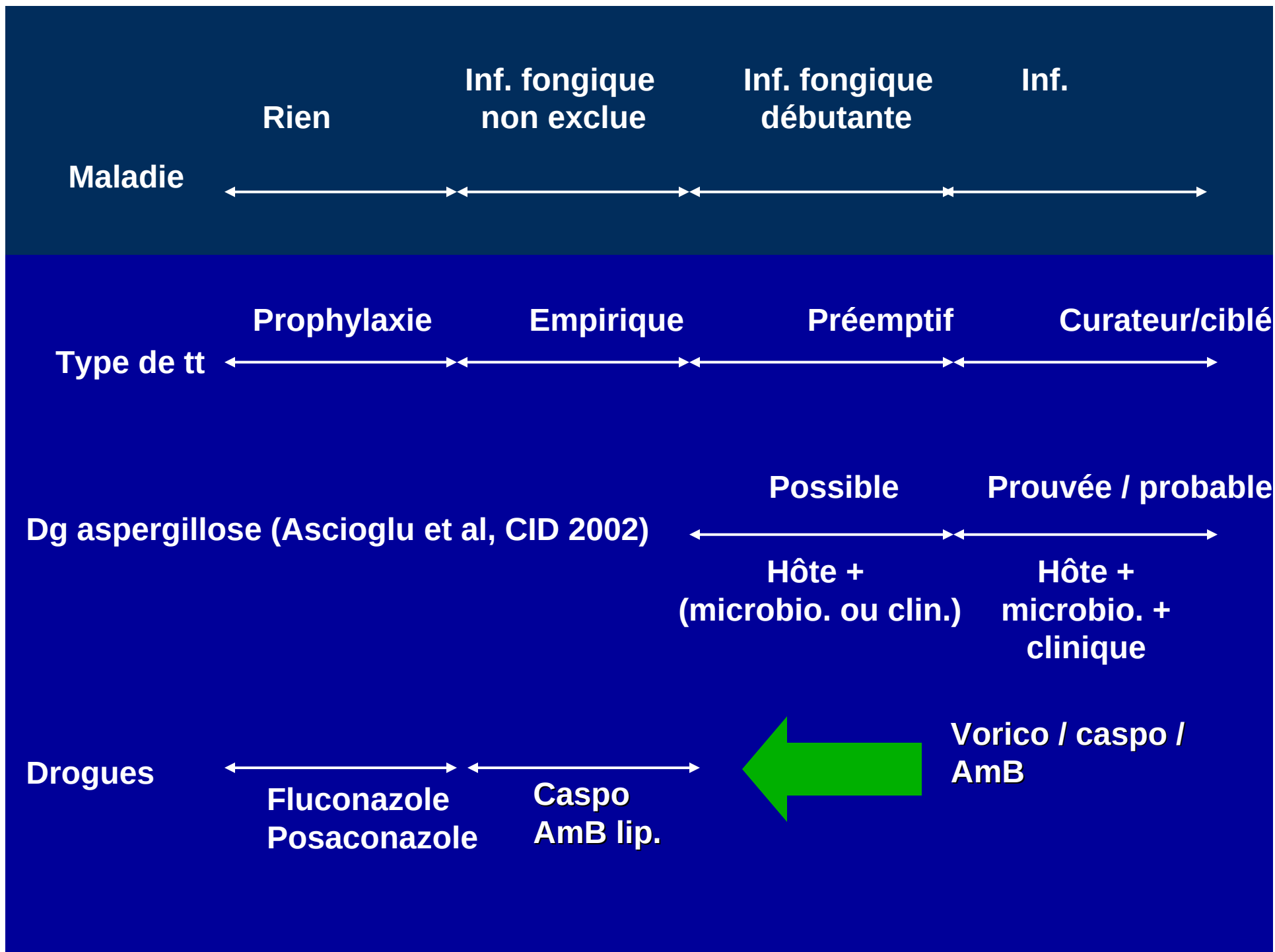
* Données MSD et Drugs 2001;61 (8) :1121-1129 ** D'après Am. J. Health Syst. Pharm, vol 58, Jul 1, 2001, 1206-1214

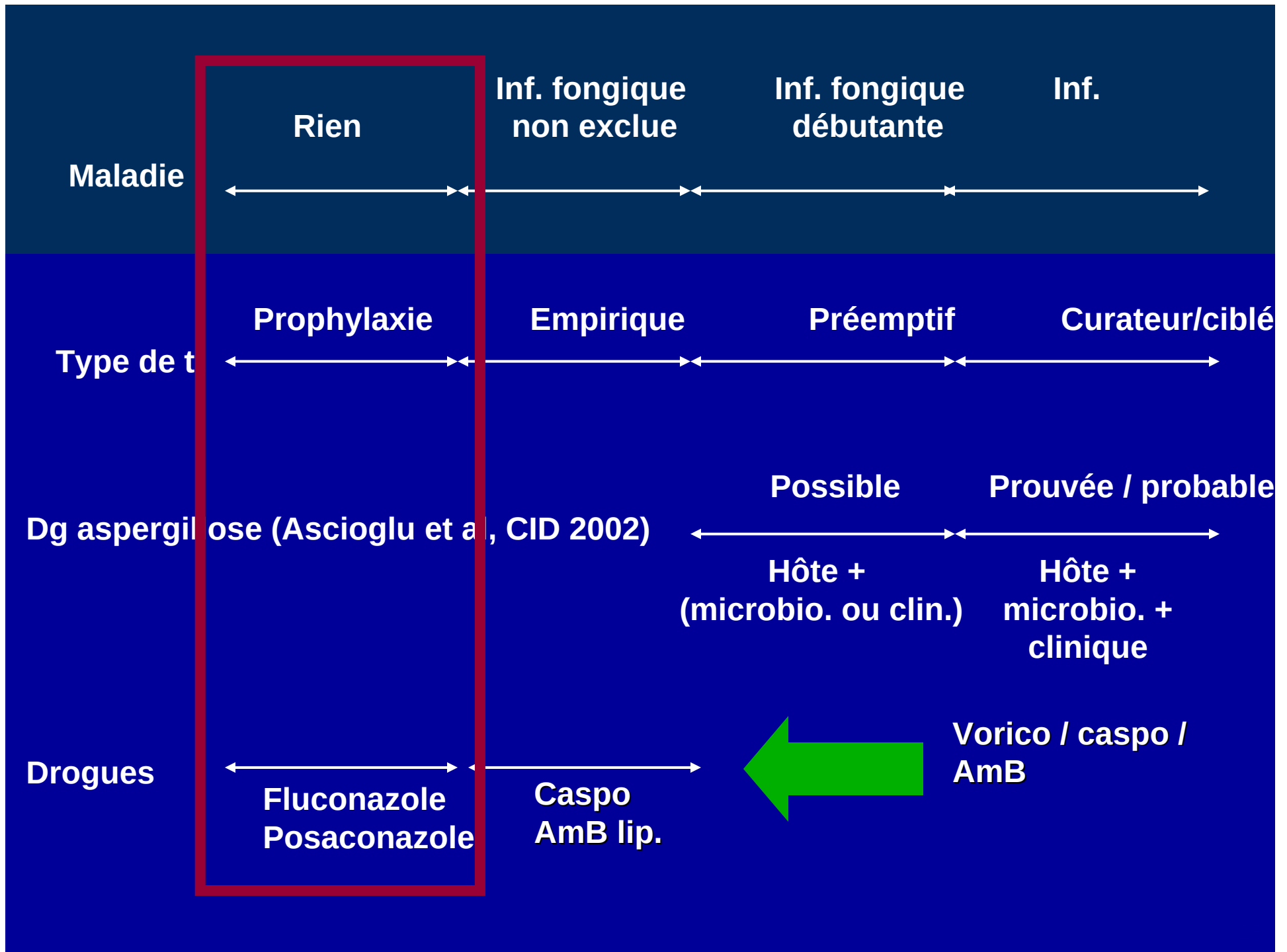
Sensibilité *in vitro* de différentes espèces de champignons aux antifongiques

	FUNGIZONE®	ANCOTIL®	TRIFLUCAN®	SPORANOX®	VFEND®	CANCIDAS®
<i>Cryptococcus</i> sp.	■	■	■	■	■	■
Zygomycetes*	■	■	■	■	■	■
<i>Fusarium</i> sp.	■	■	■	■	■	■
<i>P. boydii</i>	■	■	■	■	■	■
<i>Trichosporon</i> spp	■	■	■	■	■	■
<i>Rhizopus</i> sp et autres						



Les stratégies possibles.
Les recommandations





Posaconazole

Posaconazole

Indication selon l'AMM

Prophylaxie (1/2)

- Patients recevant une chimiothérapie d'induction-et de consolidation pour une leucémie myéloïde aiguë (LMA) ou un syndrome myélodysplasique (SMD) connus pour induire une neutropénie prolongée et qui sont à haut risque de développer des infections fongiques invasives

Posaconazole

Indication selon l'AMM

Prophylaxie (2/2)

- Receveurs de greffes de cellules souches hématopoïétiques (GCSH) sous traitement immunosuppresseur à haute-dose pour la maladie du greffon contre l'hôte et qui sont à haut risque de développer des infections fongiques invasives.

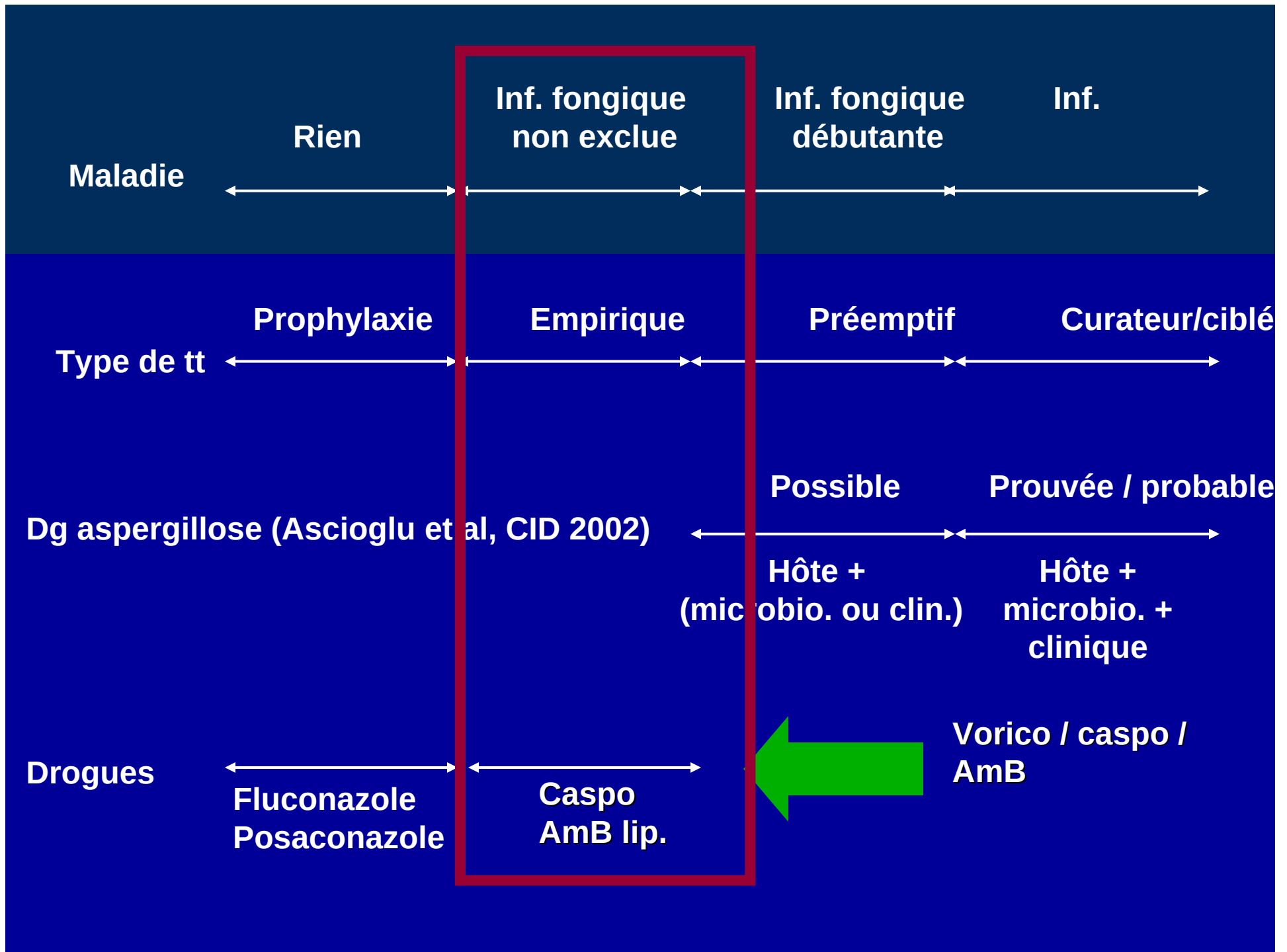
Fluconazole

BENEFICE ALLOGREFFE DE MOELLE

400mg/j → J75

	Fluconazole	Placebo	P
Incidence candidose Systémique	3%	20%	< 0,001
Décès candidose précoce (< 110 j)	1%	9%	0,001
tardif (> 110 j)	1%	8%	0,0068
GVH sévère intestinale	6%	14%	0,02
Ampho B empirique	38%	55%	0,005
Survie à 8 ans	45%	28%	0,0001

Slavin MA et al JID 1995. Marr KA et al Blood 2000

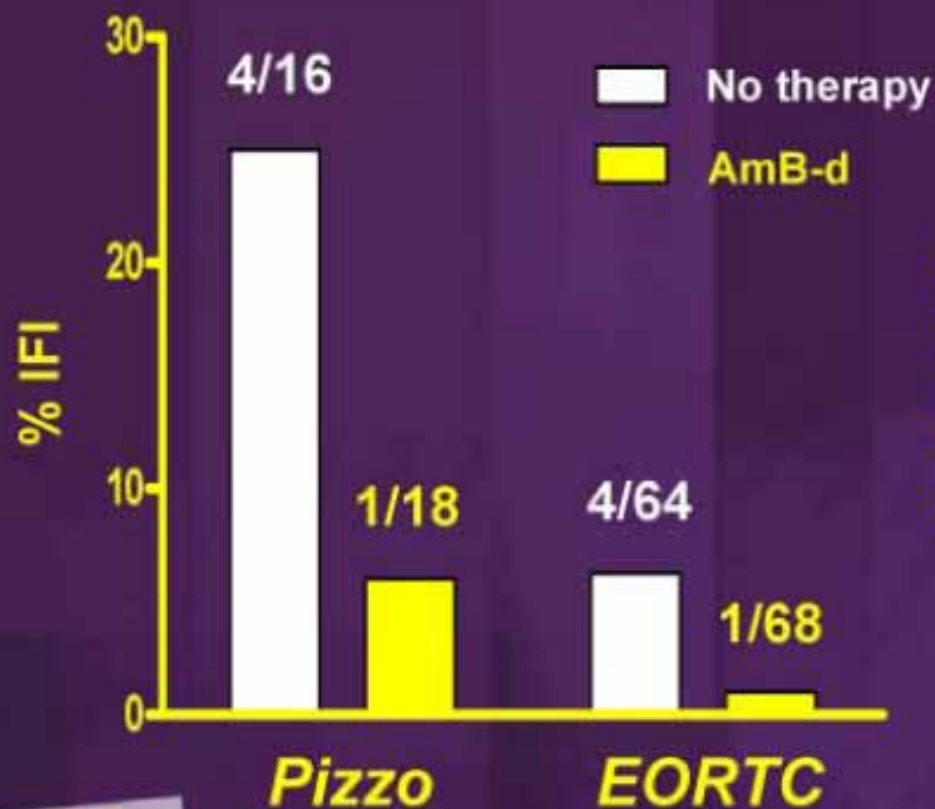


Ampho B Deoxycholate vs. No Therapy

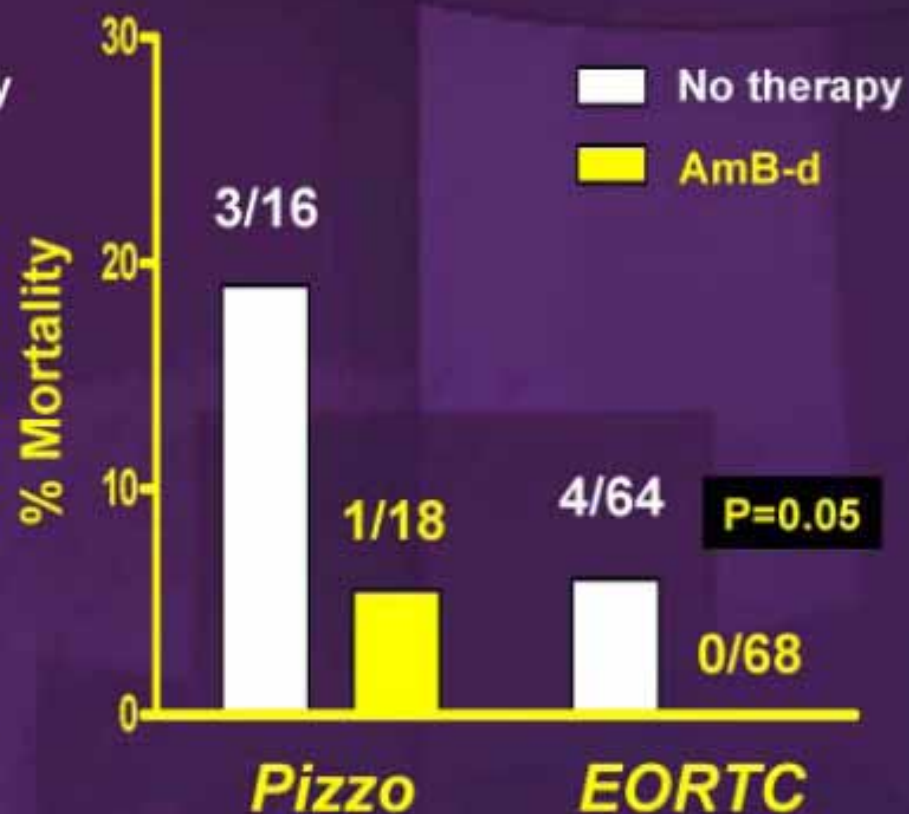
Pizzo, Am J Med, 1982; 72: 101-11

EORTC, Am J Med, 1989; 86: 668-72

Invasive Fungal Infections (IFI)



Mortality IFI



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Comparison of Two Empirical Antifungal Agents

FUO + > 38 °C during > 3-5 days (or relapsing) + Neutrophils <0.5 G/L

↓
**Open or double-blind randomization
(Stratification: Risk + Antifungal Prophylaxis)**

AMPHOTERICIN B

**OTHER FORM AMPHO B or
AZOLE or
ECHINOCANDIN**

↓
**Primary endpoint: EFFICACY (equivalence or non-inferiority) or
TOXICITY**

Assessment efficacy: COMPOSITE endpoint (3-6 criteria)

Synopsis of Clinical Trials

	Size	Design	Regimens	Primary endpoint
Prentice, 1997	338	Open	Lipo AmB 1 or 3 vs AmB-d 1	Severe toxicity
White, 1998	196	Double-Blind	ABCD 4 vs AmB-d 0.8	Nephrotoxicity
Walsh, 1999	687	Double-Blind	Lipo AmB 0.6 vs AmB-d 0.6	Equivalent efficacy ($\pm 10\%$)
Wingard, 2000	244	Double-Blind	Lipo AmB 3 or 5 vs ABLC 5	Infusion-related toxicity
Winston, 2000	317	Open	Fluco 400 vs AmB-d 0.5	Equivalent efficacy ($\pm 15\%$)
Boogaerts, 2001	360	Open	Itra 200, then 400 vs AmB-d 0.7-1	Equivalent efficacy ($\pm 15\%$)
Ehninger, 2002	162	Open	Itra 200, then 400 vs AmB-d 0.7-1	Severe toxicity
Walsh, 2002	837	Open	Vori 6, then 400 vs Lipo AmB 3	Non-inferior efficacy ($\pm 10\%$)
Walsh, 2004	1095	Double-Blind	Caspo 50 vs Lipo AmB 3	Non-inferior efficacy ($\pm 10\%$)

Overall Response (Composite Endpoint)

	EXPERIMENTAL		CONTROL		
Prentice, 1997	Lipo AmB 1	58%	AmB-d 1	49%	P=0.09
	Lipo AmB 3	64%			
White, 1998	ABCD 4	50%	AmB-d 0.8	43%	NS
Walsh, 1999	Lipo AmB 3	50%	AmB-d 0.6	49%	NS
Wingard, 2000	ABLC 5	33%	Lipo AmB 3	40%	NS
			Lipo AmB 5	42%	
Winston, 2000	Fluco 400	68%	AmB-d 0.5	67%	NS
Boogaerts, 2001	Itra 200	47%	AmB-d 0.7	38%	Δ 9 (CI -1 to 13)
Ehninger, 2002	Itra 200	63%	AmB-d 0.7	43%	P=0.0001
Walsh, 2002	Vori 6	26%	Lipo AmB 3	31%	Δ -4 (CI -11 to 2)
Walsh, 2004	Caspo 50	34%	Lipo AmB 3	34%	Δ 0 (CI -6 to 6)



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Outcome of Baseline IFI

	Endpoint	LIPO AMB		COMPARATOR		
Walsh, 1999	Success	Lipo AmB 3	9/11 (82%)	AmB-d 0.6	8/11 (73%)	NS
Walsh, 2002	Success	Lipo AmB 3	4/6 (67%)	Vori 6	6/13 (46%)	NS
Walsh, 2004	Success IFI	Lipo AmB 3	7/27 (26%)	Caspo 50	14/27 (52%)	0.04
	<i>Aspergillosis</i>		1/12 (8%)		5/12 (42%)	
	<i>Candidiasis</i>		5/12 (42%)		8/12 (67%)	
	Mortality IFI		12/27 (44%)		3/27 (11%)	0.01

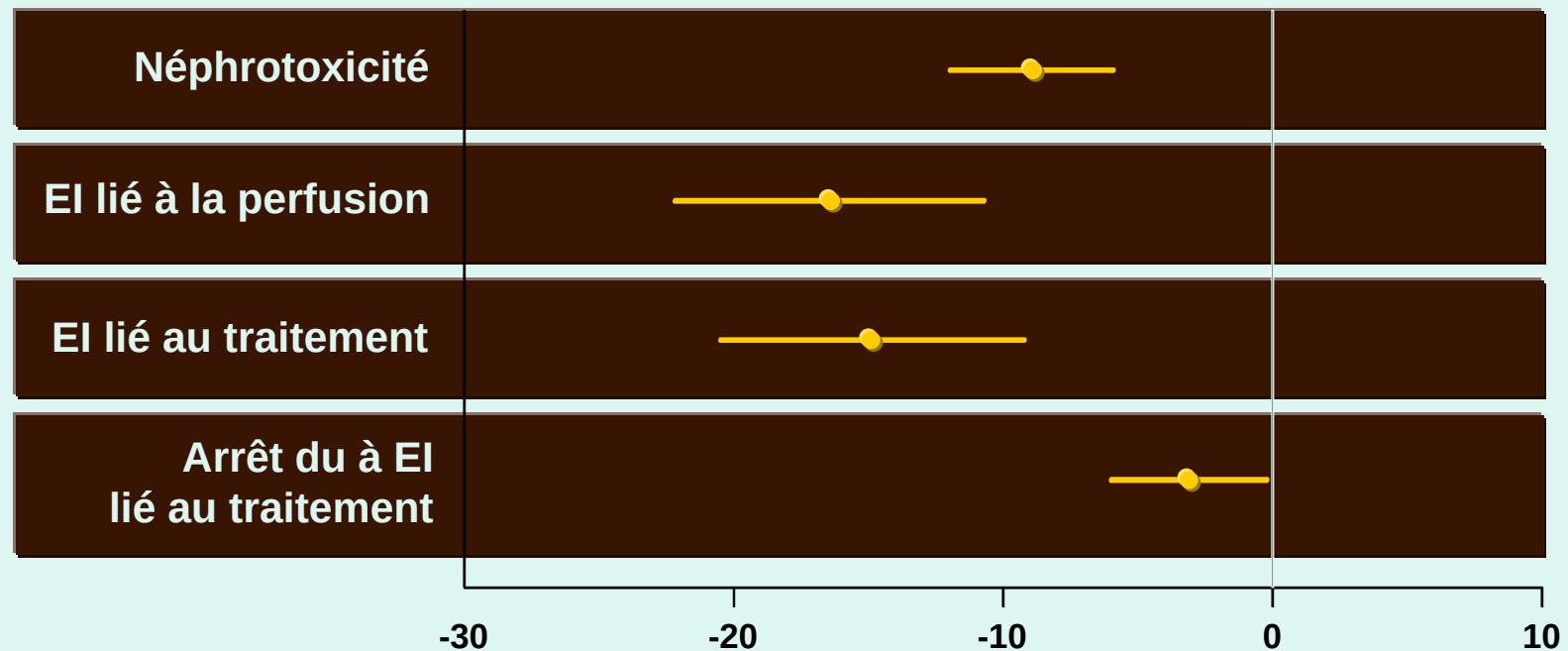
Nephrotoxicity (>2x Baseline Creatinine)

	EXPERIMENTAL		CONTROL		
Prentice, 1997	Lipo AmB 1	10%	AmB-d 1	24%	0.01
	Lipo AmB 3	12%			
White, 1998	ABCD 4	8%	AmB-d 0.8	35%	0.001
	+ Cy or Tacro	31%	+ Cy or Tacro	68%	0.001
Walsh, 1999	Lipo AmB 3	19%	AmB-d 0.6	34%	0.001
Wingard, 2000	ABLC 5	42%	Lipo AmB 3	14%	0.001
			Lipo AmB 5	15%	
Winston, 2000	Fluco 400	1%	AmB-d 0.5	33%	0.001
Boogaerts, 2001	Itra 200	5%	AmB-d 0.7	24%	0.001
Ehninger, 2002	Itra 200	4%	AmB-d 0.7	41%	0.001
Walsh, 2002	Vori 6	7%	Lipo AmB 3	8%	NS
Walsh, 2004	Caspo 50	3%	Lipo AmB 3	11%	0.001



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Critère de jugement de Tolérance (Intervalle de confiance de la différence)



Différence en %

En faveur de Candidas

En faveur d'AMB-L

in Leukemia

3. Evidence-Based Recommendations



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Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II



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Choice of 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	I	I
Voriconazole	2x 3 mg/kg iv	B ^{1,2,3}	I	I
AmB deoxycholate	0.5-1 mg/kg	B / D ⁴	I	I
Itraconazole	200 mg iv	C ^{1,3}	I	I
Fluconazole	400 mg iv	C ^{1,3,5}	I	I

¹ No activity against mucorales.

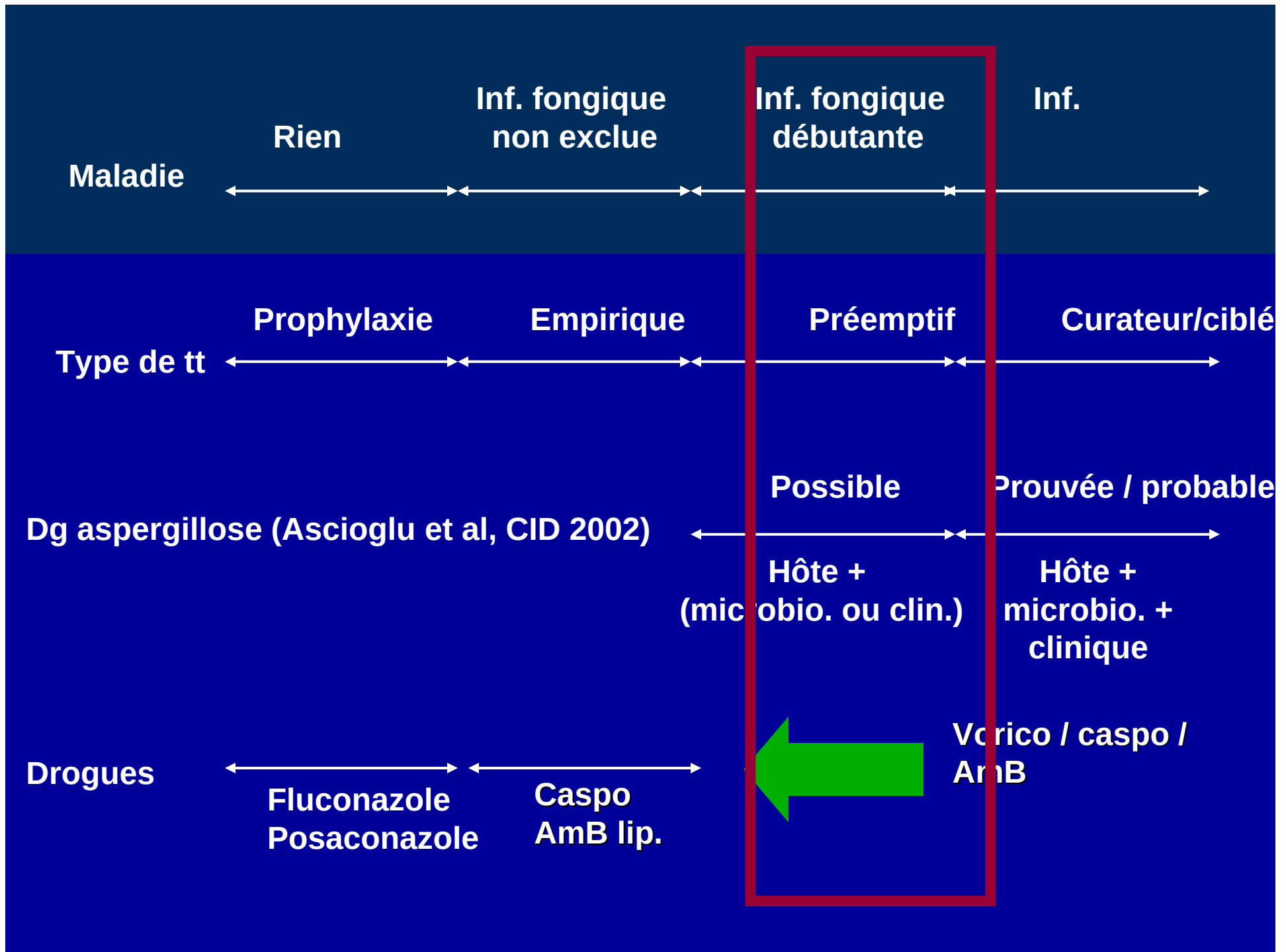
² Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis and efficacious for prevention of breakthrough IFI.

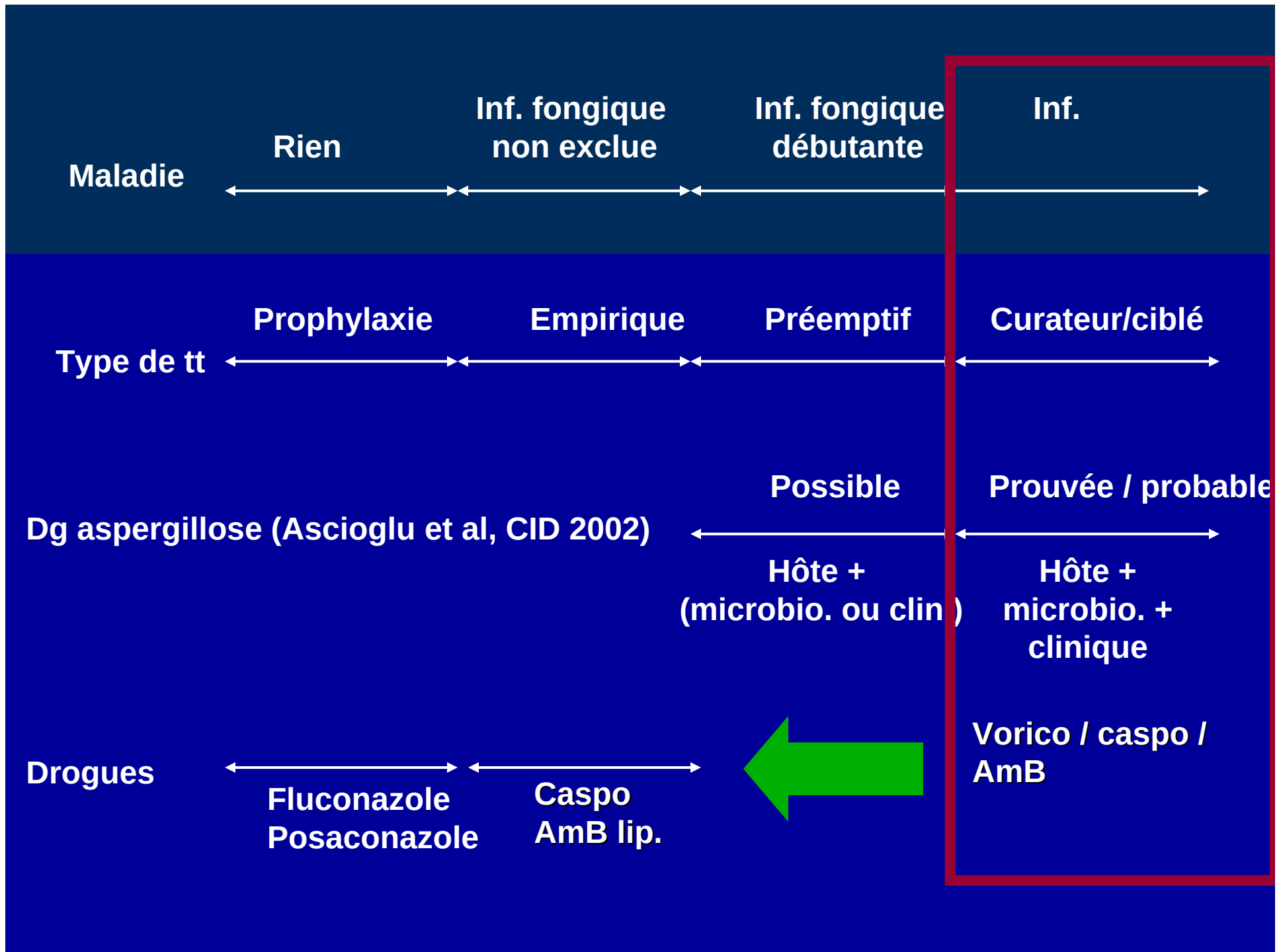
³ Activity against *Candida* may be limited in patients receiving azole prophylaxis.

⁴ B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosporin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).

⁵ No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.







Questions

- What is the optimal
 - first line antifungal therapy of candidemia / aspergillosis?
 - second line antifungal therapy of candidemia / aspergillosis?
 - duration of antifungal therapy in candidemia / aspergillosis?
- Should *in vitro* susceptibility testing be recommended to guide the choice of antifungals in candidemia / aspergillosis?
- Current indications for combination therapy in candidemia / aspergillosis ?

Aspergillosis



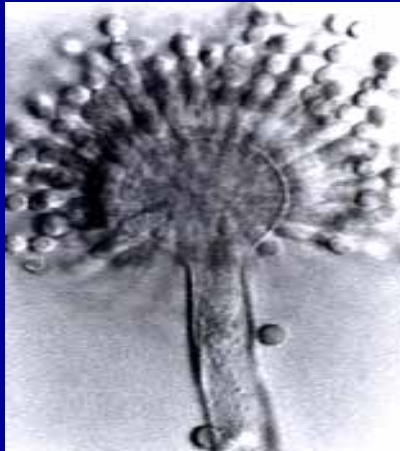
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Le tueur en série

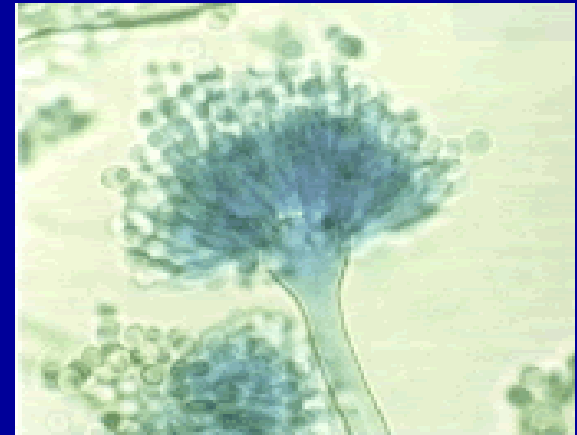
fumigatus



flavus



nidulans



terreus

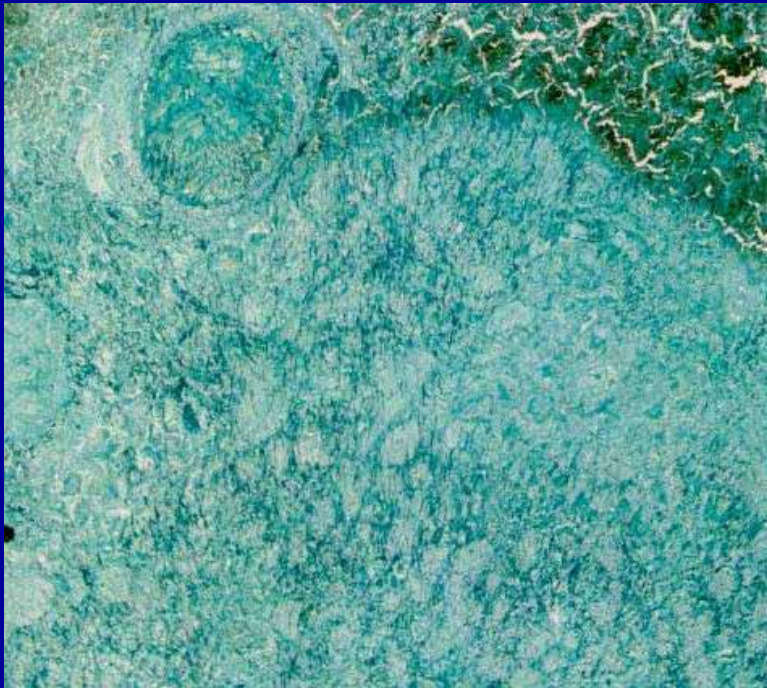


niger

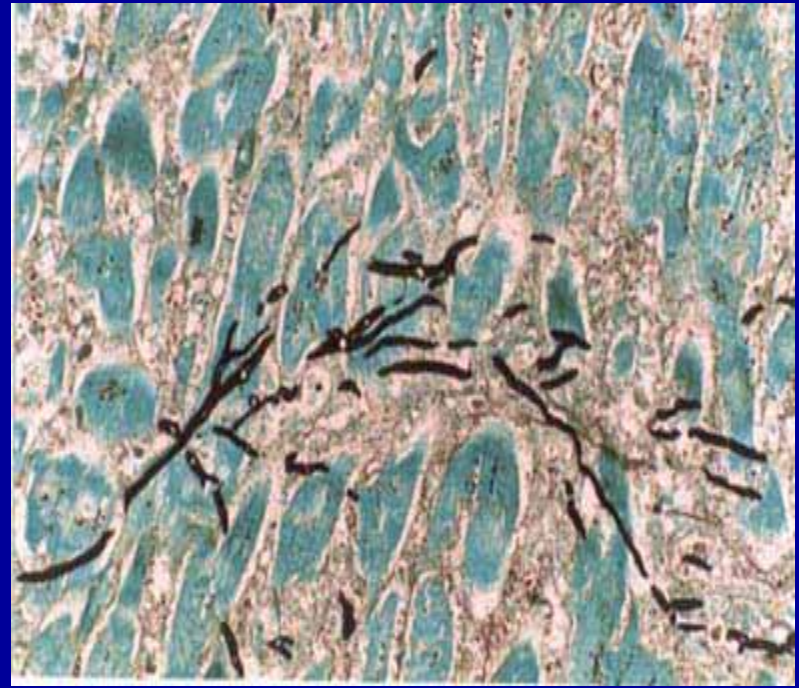


Filaments dans des biopsies

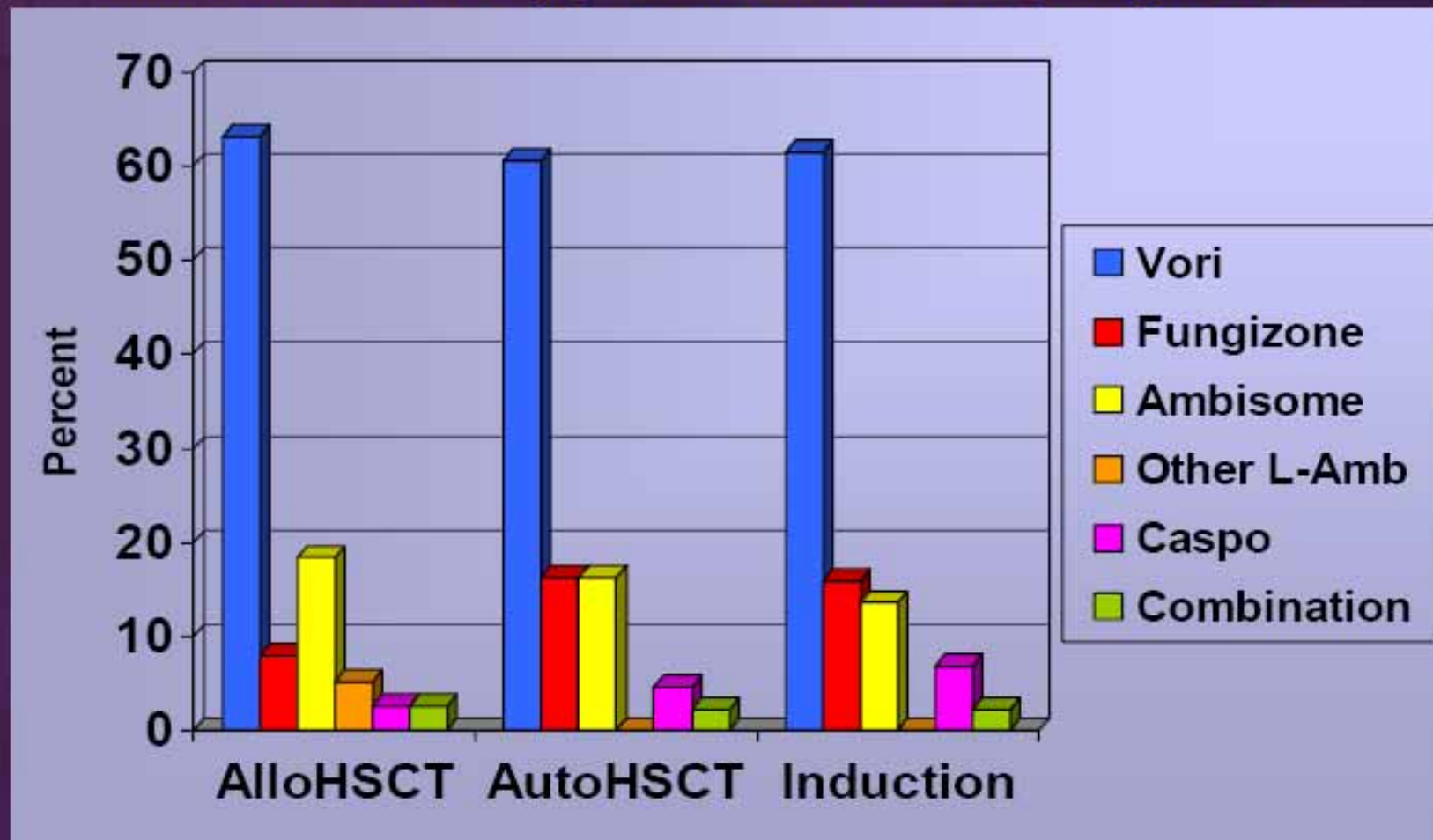
pulmonaire



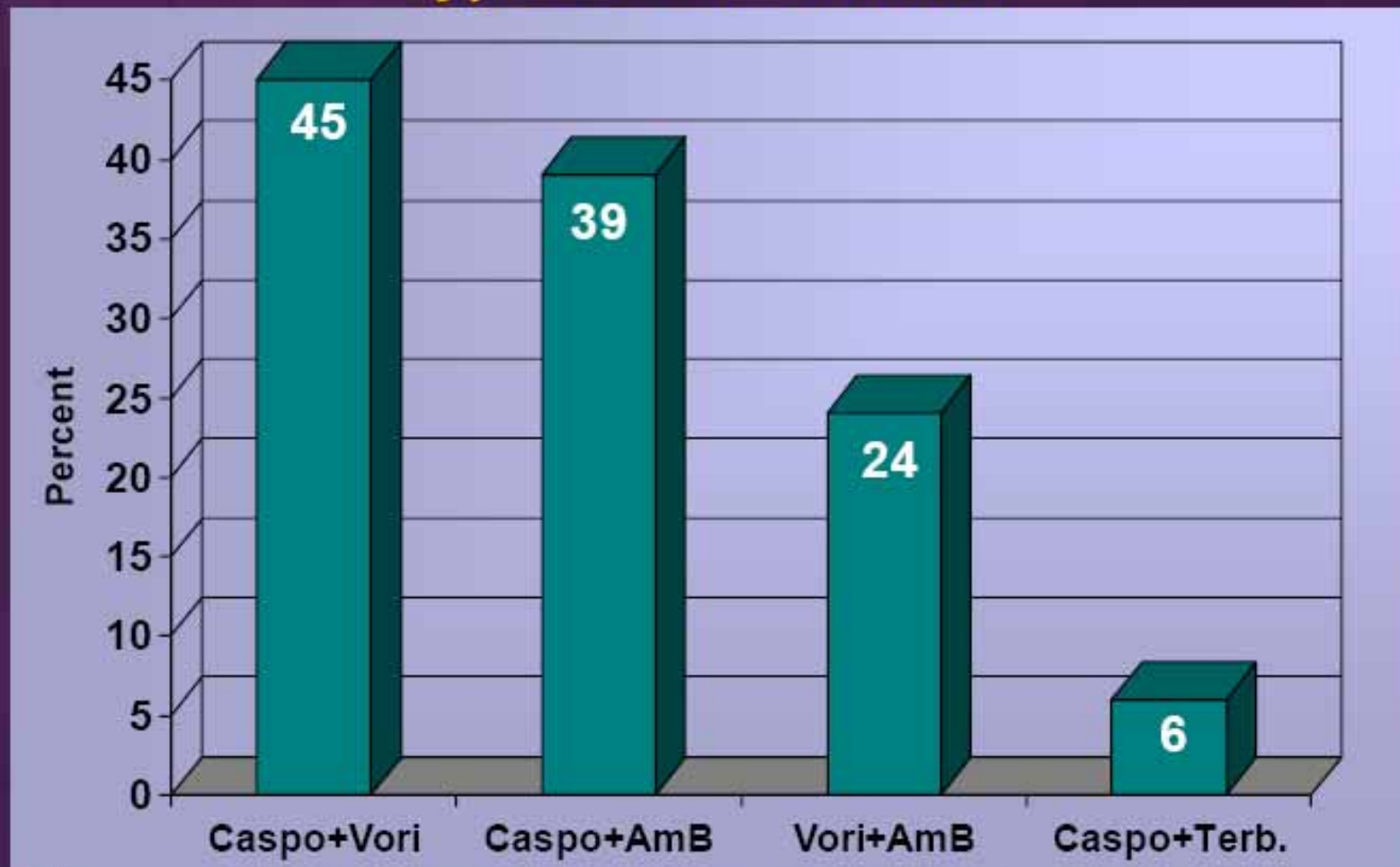
musculaire



Questionnaire on current practice (38 responses) First line therapy in invasive aspergillosis



Questionnaire on current practice (38 responses) Type of combination



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In most cases AmB = Ambisome

Results of the ECIL Questionnaire, September 2005

Questionnaire on current practice (38 responses)

Second line therapy for aspergillosis

- Equally distributed between monotherapy and combination
- For monotherapy
 - Caspofungin: 50 to 75%
 - Ambisome: 15 to 18%
 - Voriconazole: 25 to 35%
- For combination
 - Caspofungin + Voriconazole: $\approx 40\%$
 - Caspofungin + AmB: $\approx 35\%$



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Results of the ECIL Questionnaire, September 2005

Aspergillosis: Salvage combination therapy

- Vori + caspo (n=16) versus historical control group of vori alone (n=31) after failure or ampho B or itra
 - Higher 3-month survival in patients receiving combination (HR 0.42)
- Ambisome + caspo (n=31) after failure of Ambisome
 - 57% response in possible, 18% in probable or proven cases
- Ambisome (or ampho B) + caspo in possible, probable or proven aspergillosis failing ampho B
 - 18 / 30 favorable response (60%); 67% survival to discharge
- Caspo added to other antifungal agents in probable/proven cases
 - Caspo + ampho B or lipid Ampho B: 3 / 6 (50%) responses
 - Caspo + itra: 3 / 7 (43%) responses
 - Caspo + vori: 11 / 17 (65%) responses

Recommendations Aspergillosis



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Invasive pulmonary aspergillosis :1st line

Agent	Grade	Comments
Voriconazole mg/kg	A I	2 x 6 mg/kg D1 then 2 x 4 (initiation with oral: CIII)
Amphotericin B	D I	
Ambisome	B I	dose 3 – 5 mg/kg
ABLC	B II	dose 5 mg/kg
ABCD	D I	
Caspofungin	C III	
Itraconazole	C III	start with iv
Combination	D III	



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

Interactions médicamenteuses voriconazole

- Ajustement posologique de voriconazole avec :
 - Rifabutine
- Surveillance clinique et/ou ajustement posologique avec :
 - Warfarine (test de prothrombine)
 - Cyclosporine, tacrolimus (niveaux sanguins)
 - Sulfamides hypoglycémiants
 - Statines (CPK)
 - Benzodiazépines
 - Alcaloïdes Vinca
- Ajustement posologique de voriconazole et/ou du produit coadministré :
 - Oméprazole (1/2 dose d'oméprazole, pas de modification pour voriconazole)
 - Phénytoïne (contrôle des niveaux de phénytoïne et ajustement de voriconazole)

Aspergillosis

- Surgery (CIII) in case of
 - Lesion contiguous to a large vessel
 - Hemoptysis from a single lesion (embolization is an alternative)
 - Localized extrapulmonary lesion including central nervous system lesion (on case by case)



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
Itraconazole	C III	Insufficient data
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line



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Aspergillosis: unsolved questions

- **Duration of therapy**
 - **No fixed duration**
- **In vitro testing**
 - **Filamentous fungi are not routinely tested for susceptibility**
 - **No correlation between susceptibility testing and outcome**
 - ***Identification to the species level is recommended : C III***



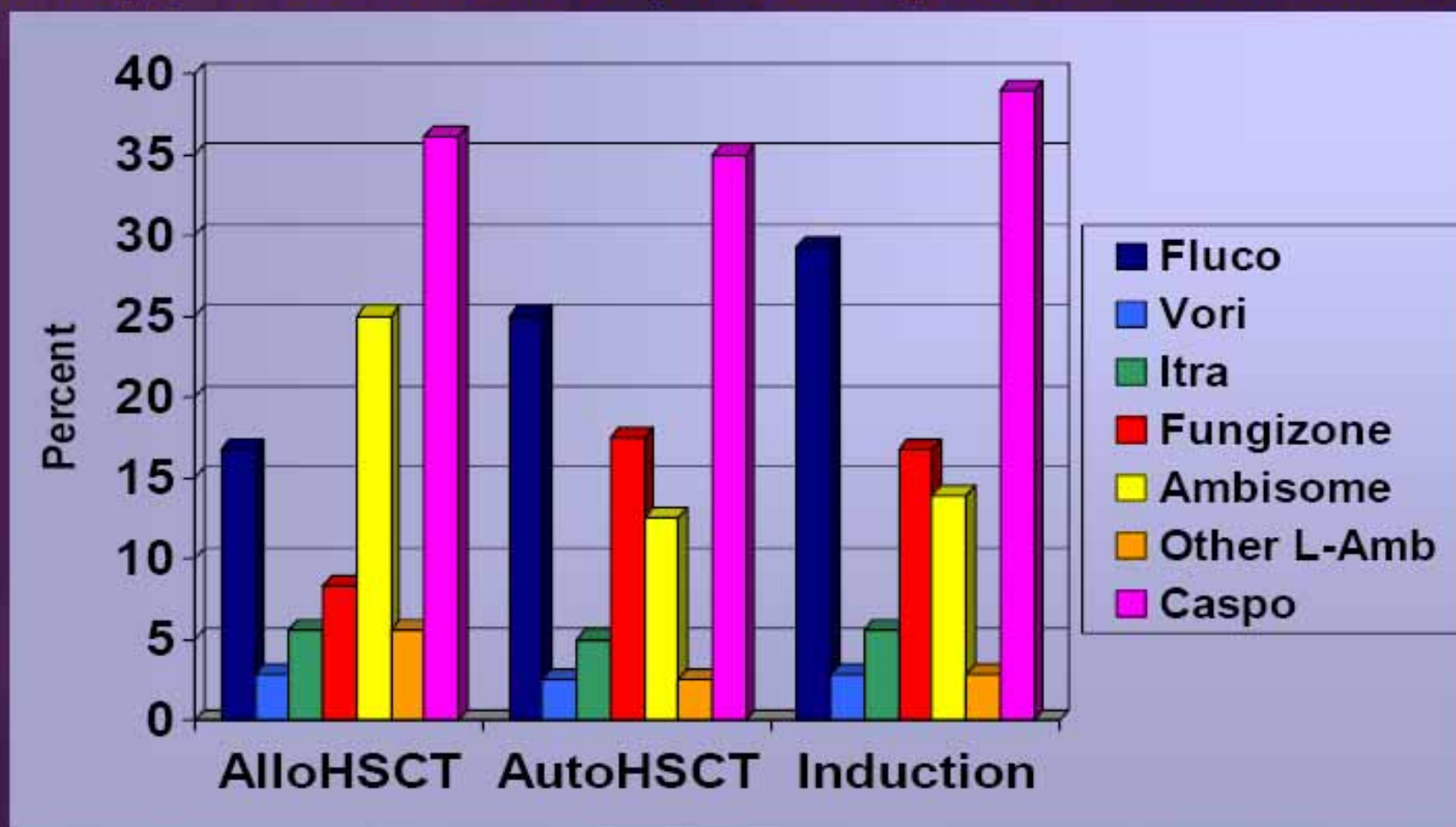
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Candidiasis



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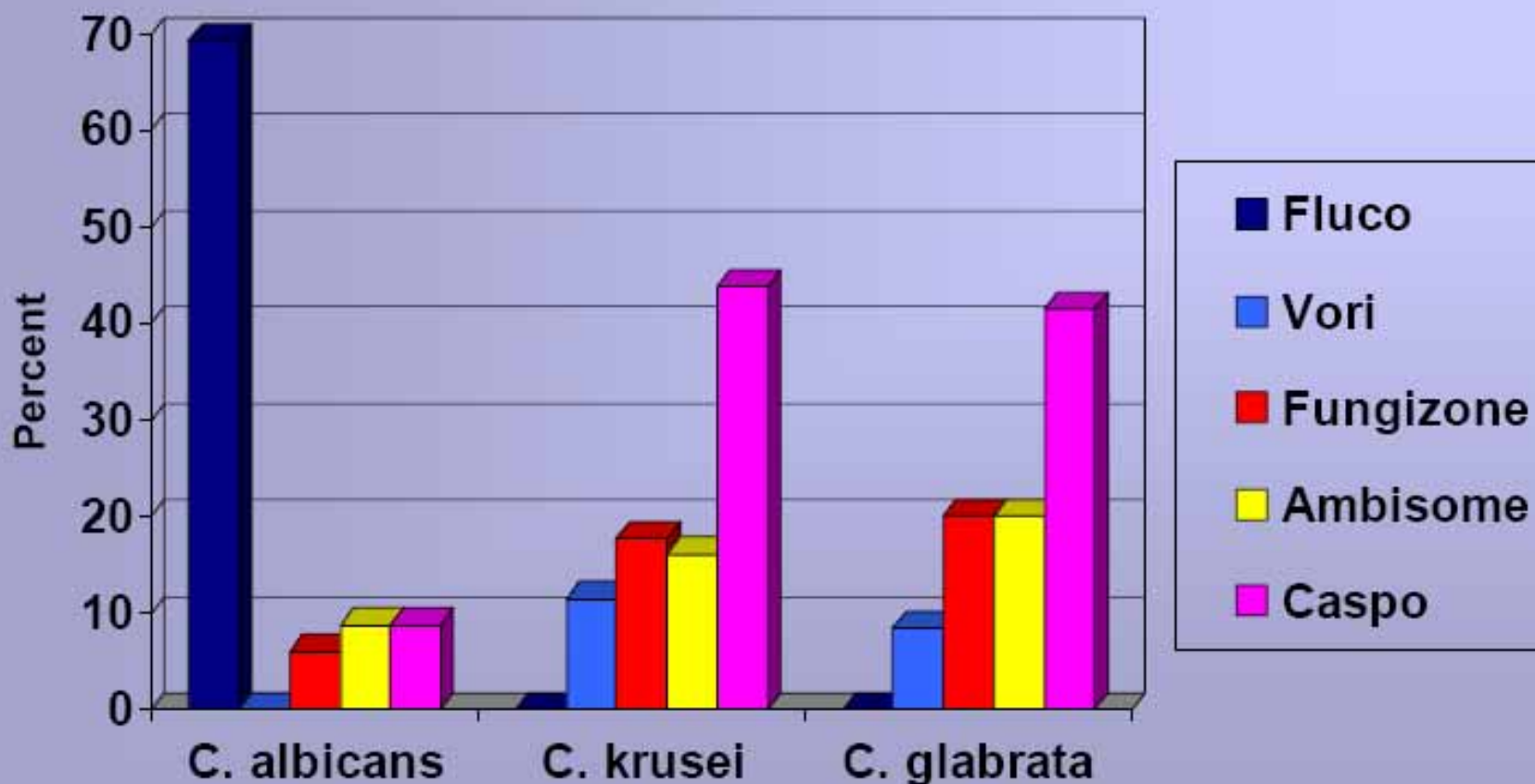
Questionnaire on current practice (38 responses) Therapy in candidemia (before species identification)



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Results of the ECIL Questionnaire, September 2005

Questionnaire on current practice (38 responses) Therapy in candidemia (after species identification)



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Results of the ECIL Questionnaire, September 2005

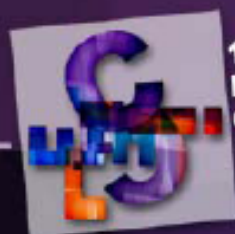
Recommendations Candidiasis



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Candidemia in hematologic pts *before identification*

Agent	General*	Comments for hematology pts
Fluconazole	A I	C III D III if azole prophylaxis or colonization with <i>C glabrata</i> E III if colonization with <i>C krusei</i>
Ampho B	A I	C III if concomitant nephrotox. drug E III if renal impairment
Lipid amphotericin B	A II	B II
Caspofungin	A I	B II
Voriconazole	A I	B II



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* Overall population at risk for candidemia not restricted to hematology or neutropenic patients

After identification: Candidemia due to *C. albicans*

Agent	General*	Comments for hematology pts
Fluconazole	A I	C III
Ampho B	A I **	C III **
Lipid amphoB	A II	B II
Caspofungin	A I	B II
Voriconazole	A I	C III

**Overall population at risk for candidemia not restricted to hematology or neutropenic patients*

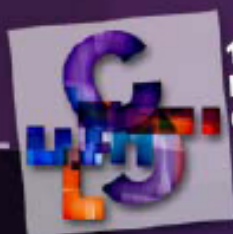
*** D III if concomitant nephrotoxic drug and E III if renal impairment*

After identification: Candidemia due to *C. glabrata* or *C. Krusei*

Agent	General*	Comments for hematology pts
Fluconazole	C III E III	D III for <i>C glabrata</i> E III for <i>C krusei</i>
Ampho B	B I **	C III** for <i>C glabrata</i> and <i>C krusei</i>
Lipd amphoB	B II	B II for <i>C glabrata</i> and <i>C krusei</i>
Caspofungin	B I	B II for <i>C glabrata</i> and <i>C krusei</i>
Voriconazole	C III B I	C III for <i>C glabrata</i> C III for <i>C krusei</i>

**Overall population at risk for candidemia not restricted to hematology or neutropenic patients*

*** D III if concomitant nephrotoxic drug and E III if renal impairment*



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Recommendations for duration of therapy in candidemia



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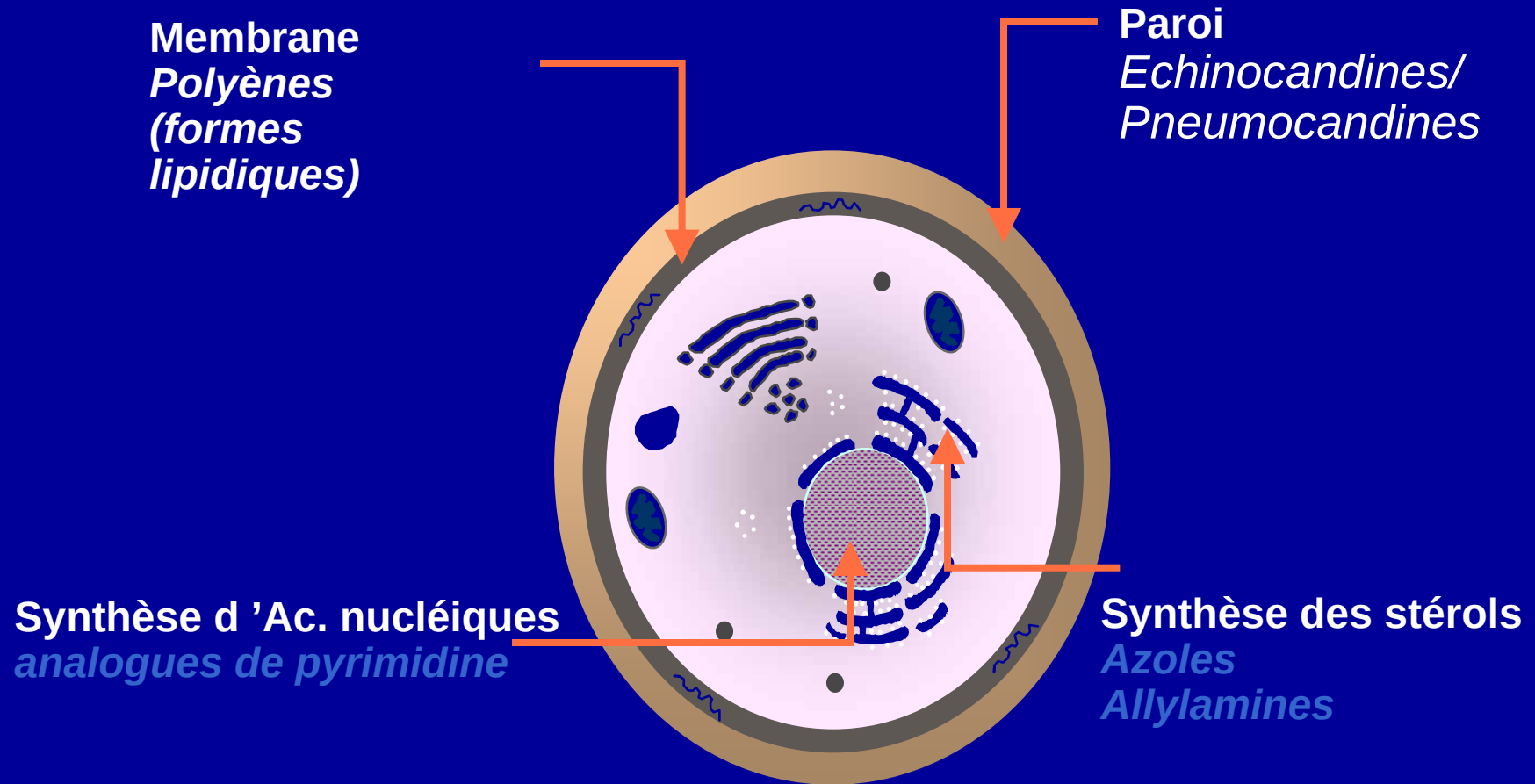
Duration of antifungal therapy in candidemia : recommendations

Non-neutropenic adults: at least 14 days after the last +ve blood culture and resolution of signs and symptoms : **B III**

Neutropenic patients: at least 14 days after the last +ve blood culture and resolution of signs and symptoms and resolved neutropenia: **C III**

Importance of an active search for dissemination of infection in leukemic patients following neutrophil recovery (ocular fundus + abdominal imaging)

Principaux antifongiques



Candidémies: pas d'antagonisme de l'association azolé+amphoB

	Fluco	Fluco+AmB	P
Succès	56%	69%	0,043
Echec/Hémoc+	17%	6%	0,02
Décès	39%	40%	NS

- Fluco 800mg/j + placebo vs Fluco + AmB (0,7 mg/kg/j)
- 60% Candida Albicans
- Toxicité rénale significativement accrue avec AmB
- Changement de cathéter: clairance significativement plus rapide
- Pas d'influence des CMI ou d'administration antérieure de Fluco

Rex JH et al CID 2003

Associations d'antifongiques: Echinocandines+amphotéricine B sur *Aspergillus* (02-04)

Association	Synergie	Indifférence	Antagonisme	Ref
Caspo+amb	+	+	0	Arikan 2002
Mica+Amb	+	+	+/-	Ostrosky ICAAC 02
Anidula+amb	+	+	+/-	Id
Caspo+Amb	0	+	0	Cuena ICAAC 03
Mica+amb	+	+	0	Laverdière TMM 03
Caspo+amb	0	+	0	Dannaoui 04

Associations d'antifongiques: Echinocandines+triazolés sur aspergillus (02-04)

Association	Synergie	Indifférence	Antagonisme	Ref
Cas+vori	+	+	0	Perea 02
Cas ou mica+Vori	+/0	+	0	Oshaugnessy/ Ghannoum ICAAC 02
Cas+itra	+	+	0	Shalit 03
Cas+Posa	+	+	0	Sabatelli ICAAC 03
Mica+Itra	+	+	+	Laverdière TMM 03

Conclusion

