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Tours et le GÉRICCO

CHRU HOPITAUX DE TOURS

Candidémies
quelle prise en charge en 2012 ?

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50 ans FACULTÉ DE MÉDECINE 1962 TOURS 2012

Définition

- ≥ 1 hémoculture positive à levure

  - identifiée comme *Candida sp.*

  - c'est une candidose invasive !!

Un problème important

- Infection nosocomiale fréquente
  - Terrain
  - Portes d'entrée
  - Facteurs de risque identifiés
- Mortalité attribuable importante
- Prolongation d'hospitalisation
- Surcoût

Optimiser la prise en charge c'est assurer:

- Un diagnostic mycologique **rapide**
- Un traitement **précoce**
  - probabiliste
- Un traitement **adapté**
  - Réévaluations thérapeutiques
- Une distinction entre formes simples / compliquées
- Une surveillance clinique prolongée
- et Savoir gérer l'échec thérapeutique

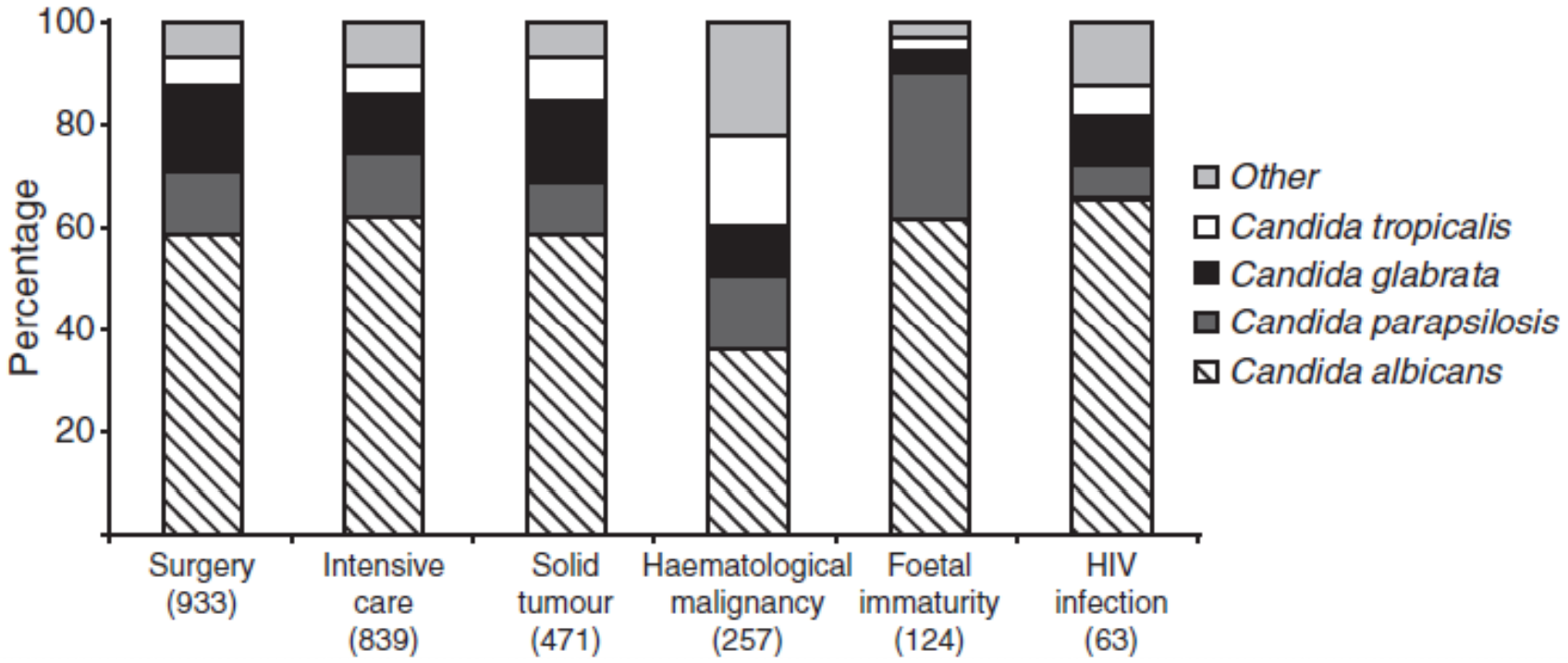
Traitement probabiliste : une prescription difficile

- le choix du traitement antifongique **probabiliste** de première intention dépend du niveau de **risque d'échec** que l'on est prêt à prendre:
  - **Arsenal thérapeutique riche**
  - **Terrain**
  - **Gravité clinique initiale**
  - **Pré-exposition aux anti-fongiques:**
    - **Azolés**
    - **Candines**
  - **Données épidémiologiques locales**

Arsenal thérapeutique riche

- **Polyènes:**
  - AmB-d IV
  - L-AmB IV
- **Pyrimidine fluorée:**
  - 5FC IV/PO
- **Triazolés:**
  - Fluconazole IV/PO
  - Itraconazole (IV)/PO
  - Voriconazole IV/PO
  - Posaconazole PO
- **Echinocandines:**
  - Caspofungine IV
  - Micafungine IV
  - Anidulafungine IV

Variations épidémiologiques



Lass-Flörl C. Mycoses 2009.

Table 2. Data on the number of episodes and the incidences of candidemia in 2000, according to patient location in the hospital, reported by 17 surveyed Swiss tertiary care hospitals.

	Hospital type					
	University		University affiliated		All	
Patient location	No. of episodes	Incidence[a]	No. of episodes	Incidence[a]	No. of episodes	Incidence[a]
Ward	45	0.47 (0.16–0.64) [b]	13	0.16 (0.06–0.57)	58	0.33 (0.06–0.64) [c]
Medical[d]	25	0.51 (0.25–1.19)[e,f]	5	0.15 (0–0.47)	30	0.39 (0–1.19)
Surgical	14	0.23 (0.09–0.64)[g]	6	0 (0–1.03)	20	0.27 (0–1.03)
Pediatric	0	0	0	0	0	0
ICU	23	1.9 (0.91–6.7)	7	0 (0–9.36)	30	2.36 (0–9.36)
Medical	9	2.5 (1.67–13.3)[h]	3	0 (0–12.3)	12	3.33 (0–13.3)
Surgical	13	2.86 (0–12)	4	0 (0–12.5)	17	3.27 (0–12.5)
Pediatric[i]	1	0 (0–0.5)	0	0	1	0.26 (0–0.5)
Overall	70[j]	0.57 (0.44–1.04)[k]	22[j]	0.35 (0.06–1.14)	92[l]	0.49 (0.06–1.14)

Incidence pour 10.000 patient/j

Environ 33-55% des candidémies survient en ICU ou en onco-hématologie

Marchetti O et al. Clin. Infect . Dis. 2004.

Table 3. General patterns of susceptibility of *Candida* species.

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R[a]
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

NOTE. I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

[a] Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

(*C. dubliniensis* & fluconazole = S to S-DD ;

C. guilliermondii & candines = S to R)

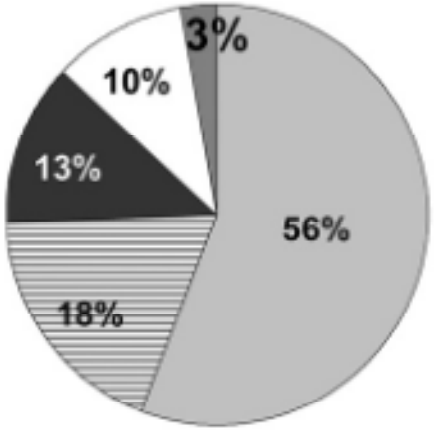
Pappas et al., CID 2009, 48 : 503-35

9

Pression de sélection des antifongiques

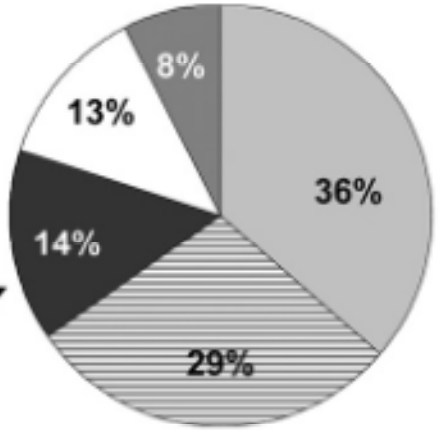
Lortholary O. et al. Antimicrob. Agents Chemother. 2001:55(2);532-38.

2002-2009: 2241 malades
2538 épisodes - 97 récurrences



sans exposition

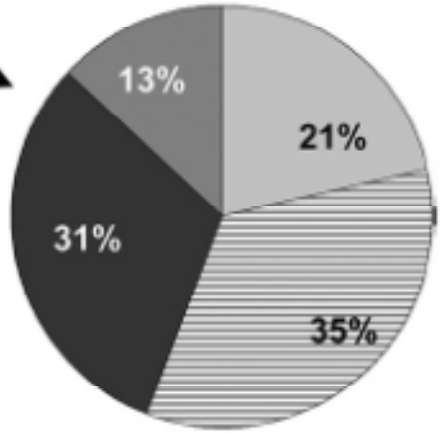
Fluconazole



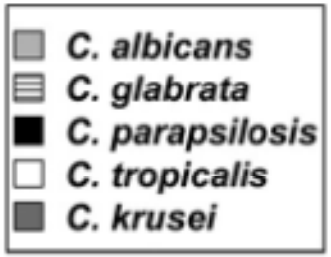
N=159

Exposition dans les 30 j

Caspofungin



N=61



Pression de sélection de caspofungine étude cas-contrôle

- Analyse multi-variée: cohorte hématologique

Paramètres	cas N=51 (%)	contrôles N=102 (%)	OR	95%CI	P
Age < 65 ans >65 ans	 45 (88.2) 6 (11.8)	 66(64.7) 36 (35.3)	 **3.81** 1	 1.26-8.5	 0.015
Caspo dans les 30 j	14 (27.5)	6(5.9)	**5.25**	1.68-16.35	0.004

CMI caspofungine > 0.5 mg/l
C.paraspilosis + C guilliermondii (43), C.albicans (2), C.glabrata, C.krusei, C.lipolytica

Blanchard E. et al. Antimicrob. Agents Chemother. 2011;55(11):5358-61.

voir poster G06
JNI 2012

2004-2010

CNRMA

20 souches
10 candidémies

100% préexposition caspofungine

Table 1. Characteristics of 20 patients with infections caused by a non–*parapsilosis/guilliermondii Candida* spp. Fks mutation, France, 2004–2010*

Patient no.	Age, y/sex	Underlying condition	Neutropenia	Species	Site of infection	Duration of caspofungin exposure, d†	Outcome at 30 d‡
1	34/M	HIV positive	No	*C. albicans*	Esophagus	21	Alive
2	20/M	Hematologic malignancy: familial lymphohistiocytosis	Yes	*C. albicans*	Blood	17	Dead
3	77/M	Hematologic malignancy: AML	Yes	*C. albicans*	Blood	25	Alive
4	46/M	Hematologic malignancy: AML	Yes	*C. albicans*	Blood, peritoneum, pleural fluid	26	Dead
5	34/F	Liver transplant: cirrhosis	No	*C. albicans*	Hepatic abscess, peritoneum	60	Alive
6	64/F	Hematologic malignancy: AML; breast cancer	No	*C. albicans*	Blood	25	Alive at 17 d
7	59/M	Teratocarcinoma	No	*C. albicans*	Pharynx	35	Dead
8	28/M	Chronic mucocutaneous candidiasis	No	*C. albicans*	Pharynx, nails	270	Alive
9	14/F	Hematologic malignancy: ALL	Yes	*C. krusei*	Lung	45	Alive
10	79/M	Hematologic malignancy: non-Hodgkin lymphoma	Yes	*C. krusei*	Blood	10	Dead
11	46/M	Hematologic malignancy: Burkitt lymphoma; HSCT	Yes	*C. glabrata*	Blood	None	Dead
12	85/M	Gastric ulcer; CVC	No	*C. glabrata*	Blood	32	Alive
13	28/M	Hematologic malignancy: non-Hodgkin lymphoma; HSCT	No	*C. glabrata*	Palate§	135	Alive
14	48/M	Esophageal cancer	No	*C. glabrata*	Blood	12	Alive
15	41/M	Liver transplant: fulminant hepatitis	No	*C. glabrata*	Blood, peritoneum	37	Dead
16	38/F	Hematologic malignancy; AML; HSCT	Yes	*C. glabrata*	Blood	51	Dead
17	60/M	Acute pancreatitis; GI tract surgery	No	*C. glabrata*	Bile	34	Alive
18	39/M	Hematologic malignancy: AML; HSCT	No	*C. glabrata*	Sinus§	15	Alive
19	55/F	Lock-in syndrome; neurogenic bladder	No	*C. glabrata*	Urine¶	27	Alive
20	63/M	Colon cancer	Yes	*C. glabrata*	Blood	14	Alive

*AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplantation; CVC, central venous catheter; GI, gastrointestinal.
†Duration of caspofungin exposure before isolation of the first resistant *Candida* isolate.
‡Outcome 30 d after isolation of the first resistant *Candida* isolate.
§From a biopsy specimen.
¶With sepsis.

Dannaoui E. et al. Emerg. Infect. Dis 2012.18(1):86-90

CMI caspo ≥ 0.5 µg/ml

C. glabrata MDR : Flu-R/candine-R un problème pour l'avenir ?

TABLE 2 Comparison of the activities of anidulafungin, caspofungin, and micafungin against fluconazole-resistant isolates of *C. glabrata* from two time periods, 2001 to 2004 and 2006 to 2010[a]

Time period (yr)	Antifungal agent	No. of isolates tested	No. (%) of isolates[b]		Reference(s)
			I	R	
2001–2004	Anidulafungin	110	2 (1.8)	0 (0.0)	27, 42
	Caspofungin	110	4 (3.6)	0 (0.0)	
	Micafungin	110	0 (0.0)	0 (0.0)	
2006–2010	Anidulafungin	162	6 (3.7)	15 (9.3)	Present study
	Caspofungin	162	6 (3.7)	15 (9.3)	
	Micafungin	162	8 (4.9)	13 (8.0)	

[a] All isolates were tested in accordance with CLSI document M27-A3 (8). Fluconazole resistance was defined as an MIC of ≥64 μg/ml.
[b] Number of isolates for which the echinocandin MICs were intermediate (I) (anidulafungin and caspofungin MIC of 0.25 μg/ml; micafungin MIC of 0.12 μg/ml) or resistant (R) (anidulafungin and caspofungin MIC of ≥0.5 μg/ml; micafungin MIC of ≥0.25 μg/ml).

Programme SENTRY

1669 souches de *C.glabrata*

162 souches **FLU-R** (CMI ≥ 64 μg/ml)

. 98.8% **Vori-R** (CMI > 0.5μg/ml)

. Caspo- anidula R :CMI ≥ 0.5 μg/ml

. Mica-R : CMI ≥0.25μg/ml

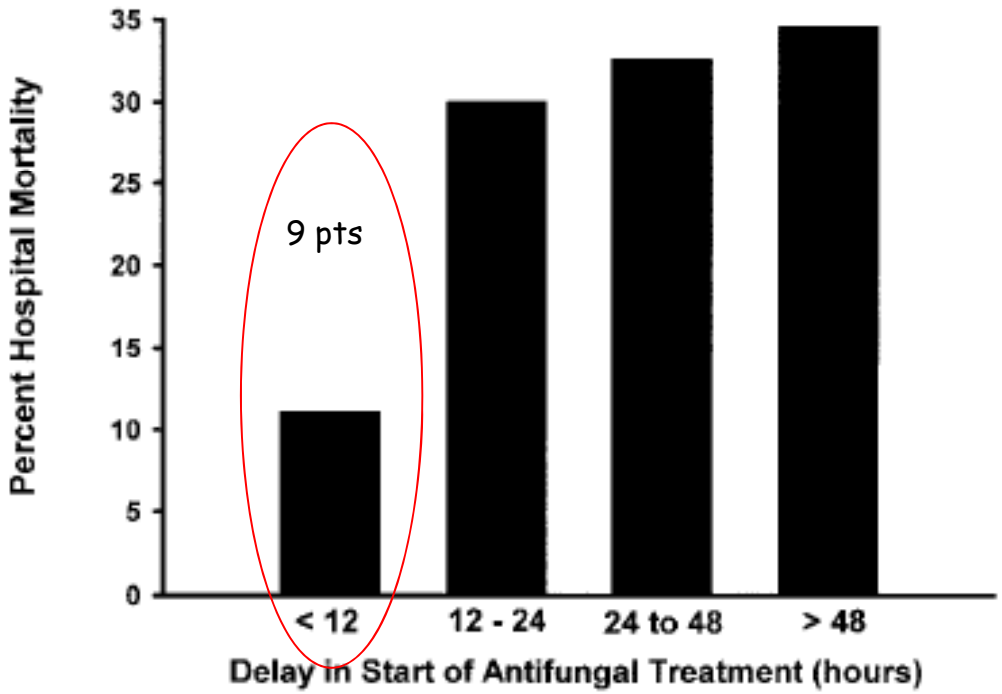
Un diagnostic microbiologique précoce: savoir y penser

- **Hémoculture positive**
  - Délai de réalisation
  - Technique de réalisation : au moins 10 ml / flacon
  - Délai de résultat
    - BacT/Alert
    - Mycosis F
  - Infection mixte: 4-29%
  - Moindre rendement chez le neutropénique

BacT/Alert

Time to detection of yeast, time to final report, and time to initiation of appropriate therapy by species of *Candida*

Fungal isolate	No. of isolates (%)	Mean time to event ± SD (h)	
		Growth detection	Final report
C. albicans	43 (43.8)	35.3 ± 18.1	85.8 ± 30.9
C. glabrata	27 (29.2)	80.0 ± 22.4	154 ± 43.8
C. parapsilosis	10 (10.4)	37.3 ± 17.0	103 ± 27.1
C. tropicalis	9 (9.38)	26.2 ± 11.1	91.6 ± 21.3
Candida dubliniensis	3 (3.13)	39.2 ± 18.1	124 ± 8.83
Candida lusitaniae	2 (2.08)	28.7 ± 13.5	77.8 ± 10.1
Candida famata	1 (1.04)	26.6	66.4
C. krusei	1 (1.04)	28.6	127



Etude rétrospective
N = 157 candidémies

Mortalité globale : 32%

Aucune donnée de sensibilité

Variable	Adjusted odds ratio	95% Confidence interval	*P* value
APACHE II score (one-point increments)	1.24	1.18–1.31	<0.001
Prior antibiotic treatment	4.05	2.14–7.65	0.028
Delay in antifungal treatment	2.09	1.53–2.84	0.018

Morrell et al. Antimicrob. Agents Chemother. 2005

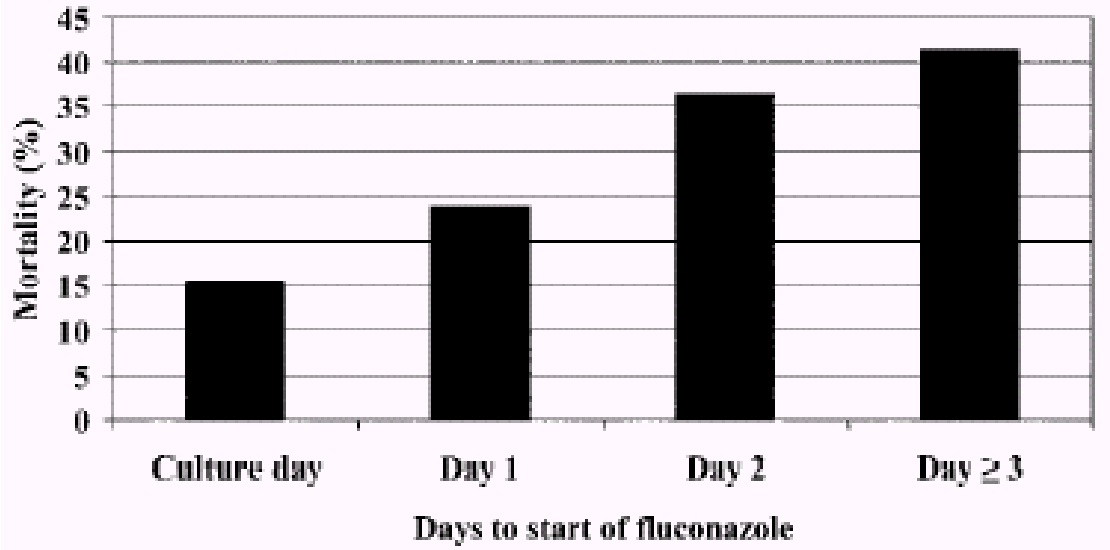


Figure 2. Relationship between hospital mortality and the number of days to initiation of fluconazole therapy. We calculated the days to the start of fluconazole therapy by subtracting the start date of fluconazole therapy from the culture date of the first blood sample positive for yeast ($P = .0009$ for trend, using the Mantel-Haenszel χ^2 test).

Etude rétrospective
Multicentrique
2002-2005

N=230 candidémies

Absence de données
de sensibilité

Mortalité hospitalière

Variable	Adjusted OR (95% CI)	*P*
Time from culture date to start of fluconazole therapy, days	1.50 (1.09–2.09)	.0138
APACHE II score, 1-point increments	1.13 (1.08–1.18)	<.001

Garey KW et al. Clin. Infect. Dis. 2006.

Bêta D glucan.

un moyen de faire un diagnostic plus précocement

Table 2 Comparison of β-D-glucan test findings from published reports.

Study group	Cutoff (pg/ml)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Febrile patients [40]	20	90%	100%	59%	97%
Candidemia/bacteremia [46]	≥80	93.3%	77.2%	51.9%	97.8%
Proven/suspected candidemia [41]	≥80	47%	100%	NS	NS
ICU patients [42]	20	NS	NS	89% (any infections)	78%
Hematological malignancy – fever [43]	≥80	86.8% (≥2 sequential tests)	81.3%	76.7%	86.5%
AML or myelodysplasia –proven/ probable IFI [44]	60	90% (1 test)≥96% (≥2 tests)	NS	NS	100%
Proven/probable IFI [45]	60	69.9%	87.1%	83.8%	75.1%
	80	64.4%	92.4%	9%	73%
Acute leukemia/neutropenia – proven/probable IFI [47]	≥7	63% (2 sequential tests)	96%	79%	91%

AML, acute myeloblastic leukemia; ICU, intensive care unit; IFI, invasive fungal infection; NS, not stated.

Autres moyens :

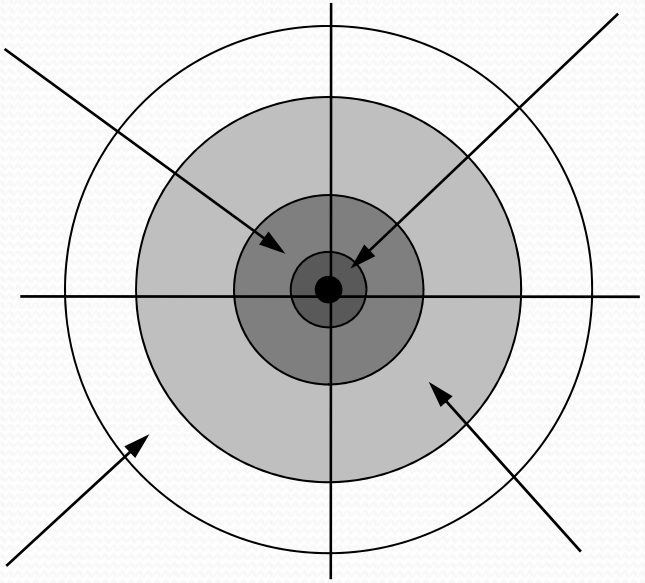
- Score de colonisation
- Candida score
- Septifast
- Traitement prophylactique chez les malades a haut risque

Ostrosky-Zeichner L et al. Medical Mycology 2011

Stratégies thérapeutiques possibles

Pre-emptive:
Laboratory tests or radiographic signs conclusive of IFI, no definitive proof by histopathology or culture

Targeted:
Definitive proof by histopathology or culture of pathogen and invasiveness of disease



Prophylactic:
No attributable signs and symptoms

Empirical:
Clinical signs and symptoms of infection, no pathogen identified

Ruping et al.

En exergue

- Toute hémoculture positive à Candida nécessite un traitement
  - Quelque soit la clinique
  - Quelque soit les facteurs de risque présents
  - Quelque soit le site de prélèvement
    - Ponction veineuse
    - Prélèvement sur cathéter/PAC

Recommandations européennes

European expert opinion on the management of invasive candidiasis in adults

B. J. Kullberg[1], P. E. Verweij[1], M. Akova[2], M. C. Arendrup[3], J. Bille[4], T. Calandra[4], M. Cuenca-Estrella[5], R. Herbrecht[6], F. Jacobs[7], M. Kalin[8], C. C. Kibbler[9], O. Lortholary[10,11], P. Martino[12]†, J. F. Meis[13], P. Muñoz[14], F. C. Odds[15], B. E. De Pauw[1], J. H. Rex[16,17], E. Roilides[18], T. R. Rogers[19], M. Ruhnke[20], A. J. Ullmann[21], Ö. Uzun[2], K. Vandewoude[22], J.-L. Vincent[23] and J. P. Donnelly[1]

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Kullberg BJ et al. Clin. Microbiol. Infect. 2011 ; 17 (suppl5):1-12

Levure: traitement probabiliste initial

- Sepsis non compliqué : stable
- Fonction rénale et hépatique normales
- Pas d'exposition antérieure aux azolés

- **Fluconazole** :

Ou

- **Candines** :
  - attention *Cryptococcus / Trichosporon*

- Réévaluation / Désescalade / Relais oral : Fluconazole

- Itra = 0, d-Amb= 0,
- Vori : pas en probabiliste ou cas particuliers

Kullberg BJ et al. Clin. Microbiol. Infect. 2011 ; 17 (suppl5):1-12

D-AmB a-t-elle encore une place dans le traitement des candidémies ?

- Moindre coût / surcoût
- Manipulation difficile
- Toxicité accrue / Terrain
  - Néphrotoxicité: OR 6.6
  - Perfusion
- Avenir : l-AmB
  - induction
  - désescalade

Kullberg BJ et al. Clin. Microbiol. Infect. 2011 ; 17 (suppl 5):1-12.
Cornely O et al. Curr. Opinion Infect. Dis. 2006;19:568-70.

Bates DW et al. Clin Infect.Dis. 2001

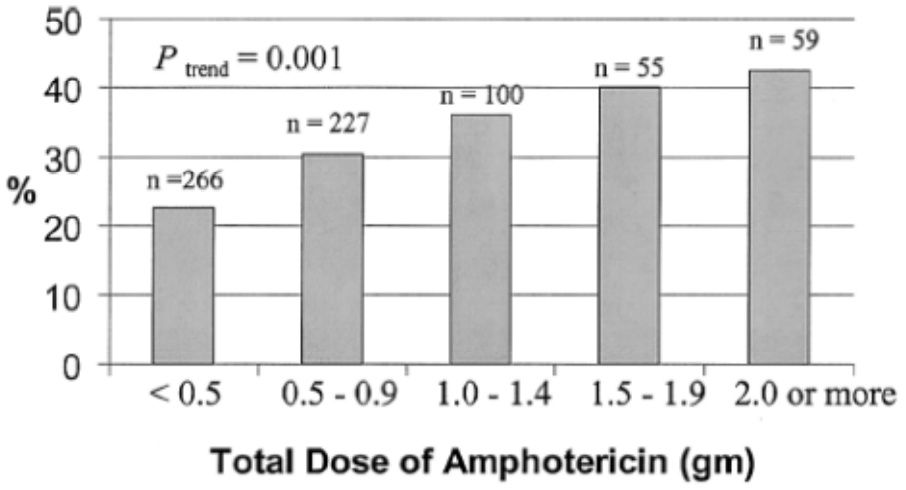

Figure 1. Percentage of patients who developed acute renal failure, according to total dose of amphotericin B.

Levure : traitement probabiliste mais en cas d'exposition antérieure aux azolés

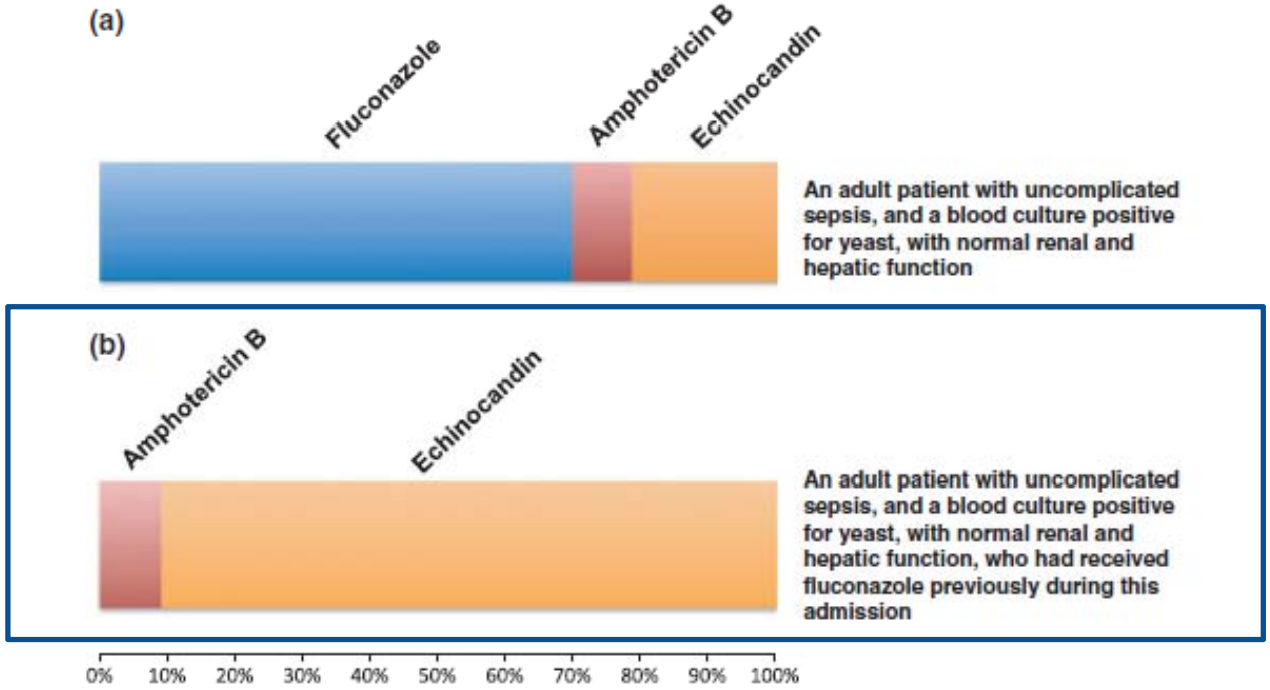

FIG. 1. Responses to the questions on initial treatment of candidaemic patients: (a) uncomplicated; (b) received fluconazole previously during this admission.

Réévaluation / Désescalade / Relais oral : Fluconazole secondairement si actif

Kullberg BJ et al. Clin. Microbiol. Infect. 2011 ; 17 (suppl5):1-12