# Associations d'antifongiques: où en est-on?

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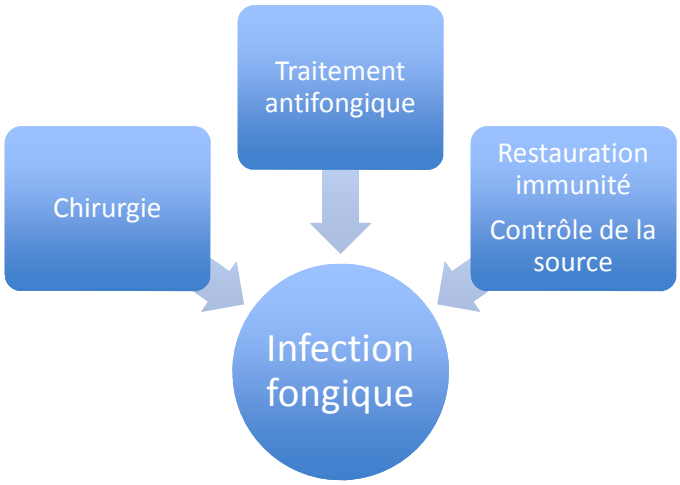
## Pourquoi prescrire une association d'antifongique?

- Infection fongique: preuve de la supériorité de l'association dans le traitement initial de l'infection:
  - Cryptococcose
- Pathogène hautement résistant aux antifongiques:
  - *Lomentospora prolificans*
- Site d'accès difficile:
  - Endocarde
  - Œil
  - Urines
- Echec du traitement par monothérapie

## Comment documenter l'intérêt d'une association d'antifongiques ?

- *In vitro*
  - Quelle méthode ?
  - Quelles définitions ?
    - Synergie/antagonisme/indifférence
- Modèles expérimentaux
  - Nombre limité d'isolats
  - Posologies utilisées suboptimales
  - ± données pharmacocinétiques
  - Traitements précoces
  - Evaluer charge fongique [cerveau]
  - Pas toujours immunodépression
- **En clinique…**

## Prise en charge d'une infection fongique



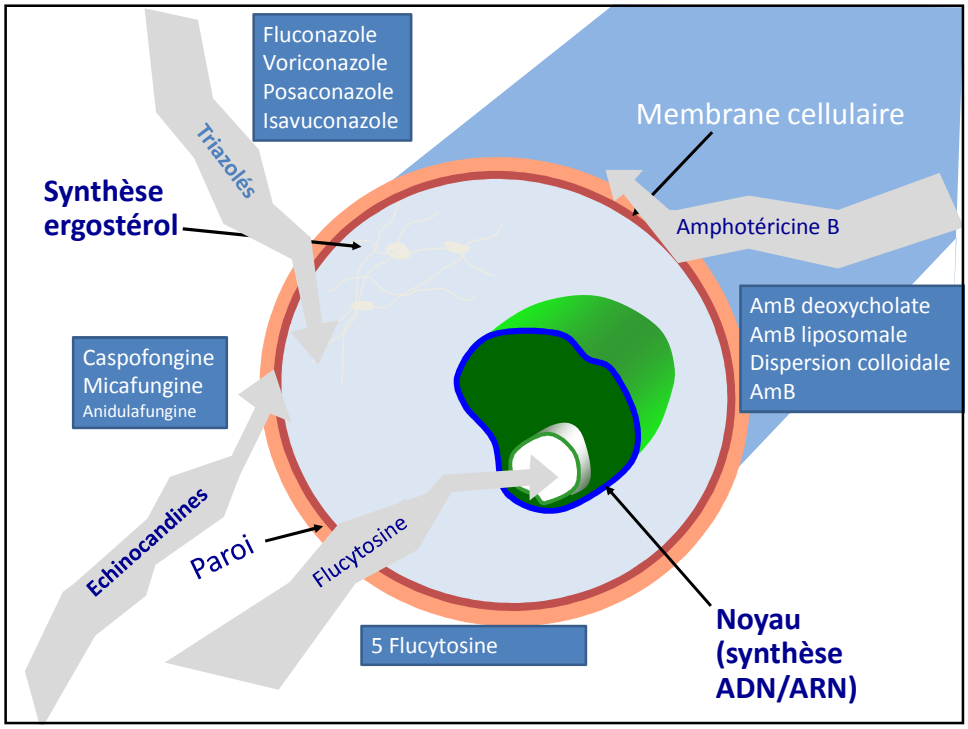
## Prescription et choix du traitement antifongique

**Immunité/** Pathologie sous-jacente
Site + sévérité de infection
Cathéter/ Porte d'entrée abdominale
Exposition antifongique

**Hôte**

**Champignon**
Genre/espèce
Résistance primaire ou secondaire
Virulence?

**Antifongique**
Choix et posologies
Pharmacocinétique
Dosage
Interactions



# Comment interpréter les CMI?

- Détermination des CMI souvent non nécessaires au plan individuelle
- Pour les Candida: élément majeur et souvent suffisant: espèce
- Souches d'Aspergillus le plus souvent sensibles
- Cryptocoque: pas d'impact des CMI sur la prise en charge sauf si préexposition
- Pour les filamenteux émergents: pas de données de corrélation entre CMI et efficacité
- Si prise en compte des CMI: en discussion avec le mycologue

# Infections à Candida

# Candidémie: FCZ + AmB?

Pas d'antagonisme chez l'homme!

- FCZ 800 mg/j + placebo [107] *vs* FCZ + AmB (0,7 mg/kg/d) [112]
- i.v. (AmB or vit) : 5-6 j; APACHE > ds groupe FCZ
- 60% *C. albicans*

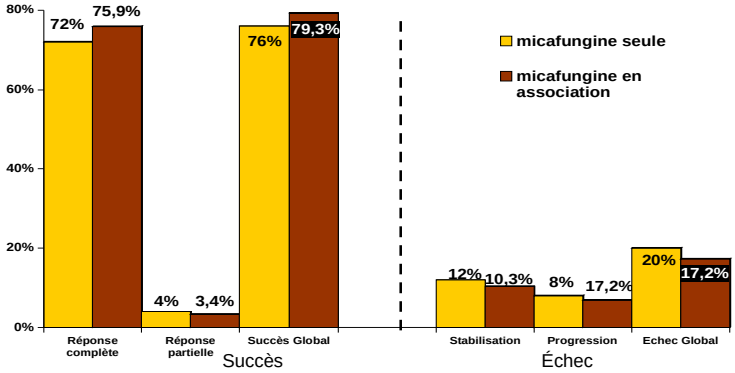
| | FCZ | FCZ + AmB | p |
|---|---|---|---|
| Succès (modèle) | 56 % | 69 % | .043 |
| Echec/HC $^{+}$ | 17 % | 6 % | .02 |
| Décès | 39 % | 40 % | NS |

- Toxicité rénale signif augmentée par AmB
- Retrait cathéter: négativation plus rapide de fongémie
- Pas d'influence des CMIs ou admin antérieure de FCZ

Rex JH et al. *CID* 2003.

# Bithérapie avec micafungine dans candidémies réfractaires

- **Ostrosky-Zeichner *et al.* (2005)**
  - Étude en ouvert, non comparative, multicentrique
  - Adulte et pédiatrique
    - <16 ans : n=14/54 (26%)
    - Neutropénie : n= 19/54 (35,1%)
  - Micafungine seule (n=25) ou en association (n=29)



# Etude prospective, randomisée comparant bithérapie AmB + 5FC vs monothérapie FCZ

| 72 patients non neutropéniques en USI | Flu 400mg J1/200mg/j n=36 | | AmB: 1-1.5 mg/kg/j +5FC 2,5gx3/j n=36 | | |
|---|---|---|---|---|---|
| | succès | échec | succès | échec | p |
| Pneumonie/ Sepsis n=55 | 18 | 10 | 17 | 10 | >0.05 |
| Péritonite n=17 | 55% guérison 86% éradication du pathogène | | 25% guérison 50% éradication du pathogène | | |

Abel-Horn et al, Infection 1996

# Recommandations ECIL-6 Première ligne

**Table 4. ECIL-6 recommendations for initial first-line treatment of candidemia.**

| | Overall population | Hematologic patients |
|---|---|---|
| Antifungal therapy | | |
| Micafungin[a] | A I | A II |
| Anidulafungin | A I | A II[b] |
| Caspofungin | A I | A II |
| Liposomal amphotericin B | A I | A II |
| Amphotericin B lipid complex | B II | B II |
| Amphotericin B colloidal dispersion | B II | B II |
| Amphotericin B deoxycholate[c] | C I | C II |
| Fluconazole[d,e] | A I | C III |
| Voriconazole[f] | A I | B II |
| Catheter removal[g] | A II | B II |

[a]See warning box in European label; [b]provisional grading; [c]close monitoring for adverse event is required; [d]not in severely ill unstable patients; [e]not in patients with previous azole exposure; [f]if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended.

**Pas de place pour les associations**

Tissot F, Haematologica 2017

Clinical Infectious Diseases
IDSA GUIDELINE

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

CID, 2016

- Endocardite à Candida
  - L-AmB 3-5mg/kg +/- flucytosine
  - Ou echinocandines forte dose
- Choriorétinite à Candida fluconazole résistant
  - L-AmB 3-5mg/kg +/- flucytosine
- Candidose du Système Nerveux central
  - L AmB 5 mg/kg/j +/- flucytosine
- Pyélonéphrite à *C. glabrata* fluconazole résistant
  - AmB-d +/- flucytosine

# Infections à Aspergillus

# Traitement de première ligne de l'aspergillose: Voriconazole et Anidulafungine

## Combination Antifungal Therapy for Invasive Aspergillosis: A Randomized Trial

- Randomized, double-blind, placebo-controlled multicenter trial.
- Voriconazole and anidulafungin vs voriconazole
- 454 patients with HM or HCT suspected or documented IA
- Primary analysis: MITT 277 patients in whom IA was confirmed
- Mortality W6 :
  - combination: 19.3% v
  - monotherapy 27.5% (P = 0.087)
- 78.7% had IA diagnosis established by CT + GM : W6 mortality combination: 15.7% vs. 27.3% (P = 0.037).

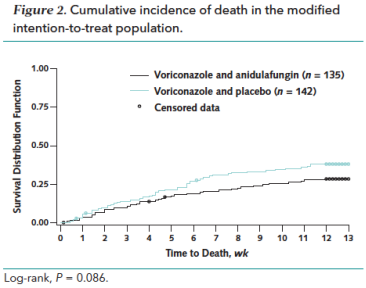
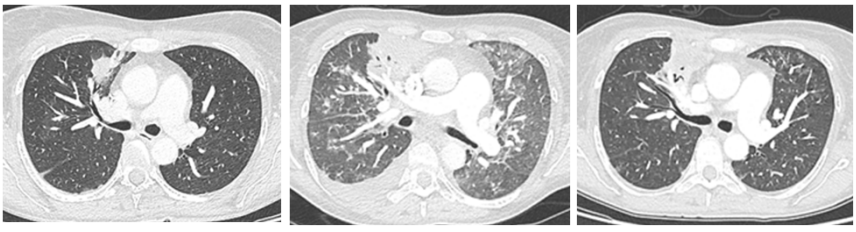



*Figure 2.* Cumulative incidence of death in the modified intention-to-treat population.

Log-rank, $P = 0.086$.

Marr K, An Int Med, 2015

# Traitement de deuxième ligne: quel timing?



J0
Aplasie post induction
LAM
Ag GM=2
Fièvre isolée
Voriconazole

J10
J2 sortie d'aplasie
Détresse respiratoire
Ag GM=1
Résiduel voriconazole=3 mg/l

J21
Ag GM=0.8

# Recommandations IDSA 2016

- Correction facteur favorisant
- 1ère ligne
  - Vfend PO ou IV (formes sévères)
  - LAmB, isavuconazole: Alternative
  - **Combinaison vori et echino peut être discutée chez des patients selectionnés**
  - Pas d'echinocandines

Recommandations Européennes ESCMID en cours

# Recommandations ECIL-6 Première ligne

Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

| | Grade | Comments |
|---|---|---|
| Voriconazole[a] | A I | Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III) |
| Isavuconazole | A I | As effective as voriconazole and better tolerated |
| Liposomal amphotericin B | B I | Daily dose: 3 mg/kg |
| Amphotericin B lipid complex | B II | Daily dose: 5 mg/kg |
| Amphotericin B colloidal dispersion | C I | Not more effective than d-AmB but less nephrotoxic |
| Caspofungin | C II | |
| Itraconazole | C III | |
| Combination voriconazole[a] + anidulafungin | C I | |
| Other combinations | C III | |
| Recommendation against use | | |
| Amphotericin B deoxycholate | A I | Less effective and more toxic |

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Tissot F, Haematologica 2017

# Recommandations ECIL-6
# Deuxième ligne

Table 8. ECIL-6 recommendations for salvage therapy of invasive aspergillosis.

| | Grade | Comments |
|---|---|---|
| Liposomal amphotericin B | B II | No data on voriconazole failure |
| Amphotericin B lipid complex | B II | No data on voriconazole failure |
| Caspofungin | B II | No data on voriconazole failure |
| Itraconazole | C III | Insufficient data |
| Posaconazole[a] | B II | No data on voriconazole failure |
| Voriconazole[a] | B II | If not used in first-line |
| Combination | B II | Various studies and conflicting results |

[a]Monitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

Tissot F, Haematologica 2017

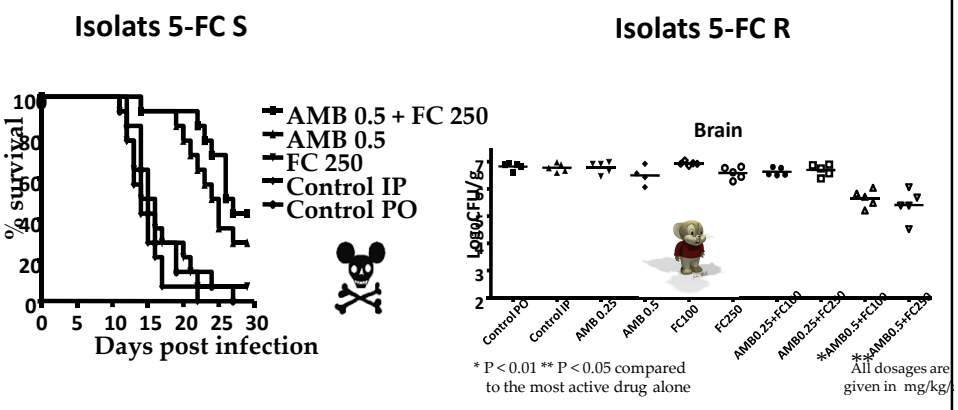
# Infections à Cryptocoque

## Interaction 5-FC et autres antifongiques sur isolats cliniques de *C. neoformans*

| Mode of interaction | % of isolates | | | | |
|---|---|---|---|---|---|
| | 5FC + FCZ (n=30) | 5FC + ITZ (n=25) | 5FC + VRZ (n=30) | 5FC + AMB (n=30) | 5FC + CAS (n=30) |
| Synergistic | 77 | 60 | 80 | 77 | 67 |
| Additive | 23 | 40 | 20 | 23 | 33 |
| Antagonistic | 0 | 0 | 0 | 0 | 0 |

Schwartz et al. AAC 2003

## Synergie de AmB + 5FC si *C. neoformans*




Schwarz, AAC 2006

## Associations dans cryptococcose

- Étude randomisée réalisée en Thaïlande
- 64 patients VIH avec 1er épisode de méningite à cryptocoque
- 4 bras de 16 patients :
  - Ampho B 0,7 mg/kg/jour
  - Ampho B + 5FC 100 mg/kg/jour
  - Ampho B + Flu 400 mg/jour
  - Ampho B + 5FC + Flu
- Pendant 2 semaines puis Flu 400 mg/jour pendant 8 semaines
- Suivi par PL itératives et compte des CFU par ml de LCR

- **Ampho B + 5FC = activité fongicide la plus rapide**
- Ampho B + Flu + 5FC aussi efficace  Ampho B + Flu

A.E. Brouwer et al. Lancet 2004.

## Stratégie thérapeutique optimale? Impact de la cohorte Crypto A/D

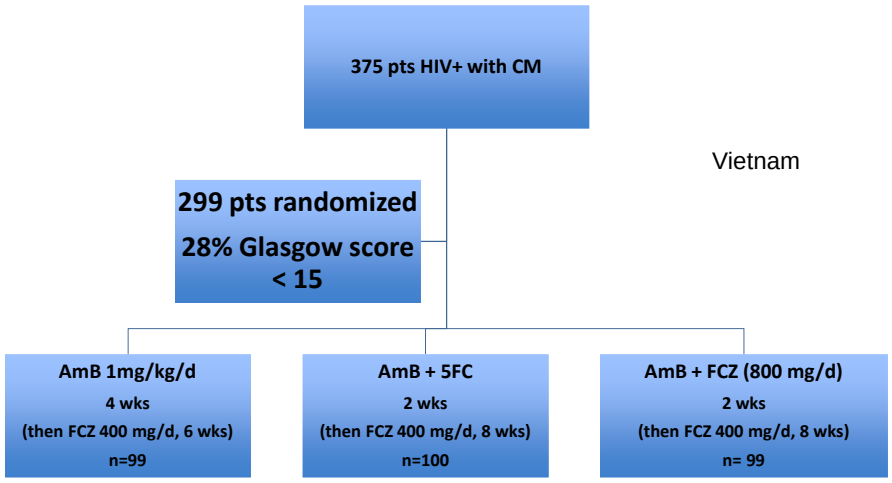
- 208 patients: analyse des échecs (décès ou échec mycologique) à S2 et M3

- **AmB + 5FC :** meilleure stratégie si méningoencéphalite, charge fongique élevée et anomalies neurologiques (26% échec vs. 56% si autres stratégies, p<0,001)

- **Prescription de 5FC pour moins de 14j** (OR =3.30[1.12-9.70], p = 0.030) indépendamment associés à échec à M3.

Dromer et al. PLoS ONE 2008

# Combination therapy with AmB during CM




Vietnam

Day N Engl J Med Apr 20

# Combination therapy with AmB during CM

| Outcome | Group 1, Amphotericin B (N=99) | Group 2, Amphotericin B and Flucytosine (N=100) | Group 3, Amphotericin B and Fluconazole (N=99) |
|---|---|---|---|
| **Coprimary outcomes** | | | |
| Death by day 14 | | | |
| No. of deaths | 25 | 15 | 20 |
| Probability of survival (95% CI) | 0.75 (0.67 to 0.84) | 0.85 (0.78 to 0.92) | 0.80 (0.73 to 0.88) |
| Death by day 70‡ | | | |
| No. of deaths | 44 | 30 | 33 |
| Probability of survival (95% CI) | 0.56 (0.47 to 0.66) | 0.69 (0.61 to 0.79) | 0.67 (0.58 to 0.77) |

**Survival benefit of AmB + 5FC vs AmB monotherapy**

Day 14: HR (for death) 0·57; 95% CI (0.30 to 1·08), p=0·08

**Day 70: HR 0·61; 95% CI (0·39 to 0·97), p=0·04**

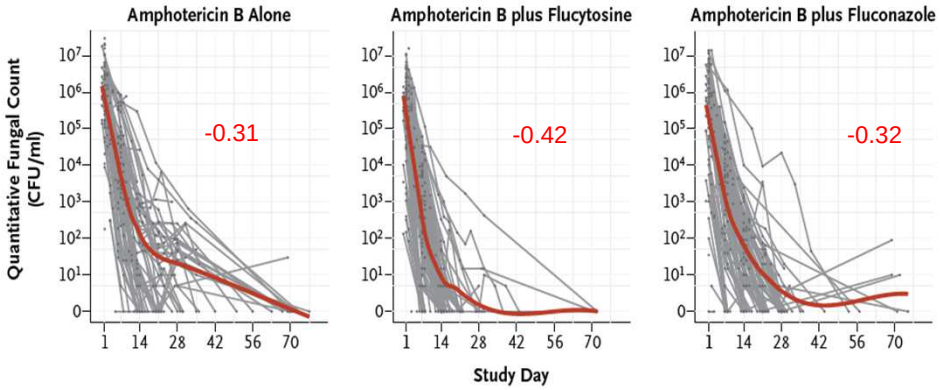
**No survival benefit of AmB + FCZ vs AmB monotherapy**

Day 14: HR 0·78; 95% CI (0.44 to 1·41), p=0·42

Day 70: HR 0·71; 95% CI (0·45 to 1·11), p=0·13

Day N Engl J Med Apr 20

# AmB + 5-FC :
## « efficiently killing a sugar-coated yeast »




**Greater rate of infection clearance (log 10 CFU/mL/d) for AmB+5-FC vs others (p<0.001)**

Day N Engl J Med Apr 20

# AmB + 5-FC : cornerstone therapy of AIDS CM

- 6 months (after adjustment for baseline covariables):
  - **Significantly higher survival in AmB +5 FC** vs AmB and AmB + FCZ
  - No difference between AmB + FCZ and AmB
  - **Significantly less disability in AmB + 5FC** vs AmB

Day N Engl J Med Apr 201

| | | |
|---|---|---|
| AmBd (0.7–1.0 mg/kg per day) or lip[illegible]mB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucyt[illegible]rant patients) | 4–6 weeks | B-II |


MRC Medical Research Council

**Randomised phase III trial** comparing **FCZ + 5FC vs. two AmB strategies** during **1 or 2 wks for** the initial treatment of AIDS-associated cryptococcal meningitis

**MRC funding:**
**Thomas Harrison**, **Angela Loyse**, St George's University, London
**Robert Heyderman, David Laloo**,Camilla Rothe, Blantyre, Malawi
**Charles Van der Horst**, Mina Hosseinipour, Lilongwe, Malawi
**Peter Mwaba**, Clarence Chiluba, Lusaka, Zambia

**ANRS funding:**
**Olivier Lortholary**, Inst Pasteur, CNRS URA3012, Hôp Necker Enfants malades, Paris
**Charles Kouanfack**, **Estelle Pasquier**,Hôpital Central & UMI233, Yaoundé, Cameroon
**Elvis Temfack, Yacouba Mapoure**, Hôpital Général, Douala, Cameroon
**Eric Delaporte**, UMI233, IRD, Montpellier

**Statistician + Data Management**
**Shabbar Jaffar**, London School of Tropical Medicine


MRC Medical Research Council

Open, phase 3 randomised non-inferiority trial, 680 pts

✓ **Induction therapy :**

- AmB (1 mg/kg/d) **7 d** + FCZ 800 mg/d or 5-FC (100 mg/kg/d)
- AmB (1 mg/kg/d) **14 d** + FCZ 800 mg/d or 5-FC (100 mg/kg/d)
- FCZ 1200 mg/d + 5-FC (100 mg/kg/d)

✓ **Then:**

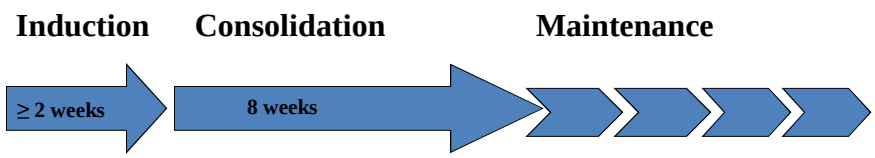
- FCZ 800 mg/d until HAART initiation (2-4 wks) then
- FCZ 400 mg/d until wk 10 followed by FCZ 200 mg/d

✓ **Primary end point :**

- Mortality at 2 wks of induction therapy

# Global therapeutic strategy of AIDS-associated cryptococcal meningitis in 2014

**(Western world; AI)**




| Induction | Consolidation | Maintenance |
|---|---|---|
| AmB 0.7-1 mg/kg/d<br>+<br>5-FC 100 mg/kg/d | Fluconazole 400 mg/d | Fluconazole 200 mg/d until immune reconstitution |

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

John R. Perfect,[1] William E. Dismukes,[2] Francoise Dromer,[11] David L. Goldman,[3] John R. Graybill,[4] Richard J. Hamill,[5] Thomas S. Harrison,[14] Robert A. Larsen,[6,7] Olivier Lortholary,[11,12] Minh-Hong Nguyen,[8] Peter G. Pappas,[2] William G. Powderly,[13] Nina Singh,[10] Jack D. Sobel,[10] and Tania C. Sorrell[15]

Baseline *C. neoformans* MIC values not predictive of outcome [Dannaoui AAC 2006]

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Guidelines for Management of Cryptococcosis • CID 2010:50 (1 February) • 000

# Bithérapie et cryptococcose

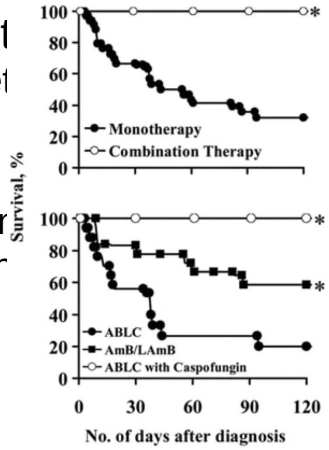
| | | | |
|---|---|---|---|
| Induction therapy | VIH+ avec méningite | | |
| AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a] | | 2 weeks | A-I |
| Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a] | | 2 weeks | B-II |
| AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients) | | 4–6 weeks | B-II |
| Alternatives for induction therapy[b] | | | |
| AmBd plus fluconazole | FCZ 800 mg/j | … | B-I |
| Fluconazole plus flucytosine | FCZ ≥ 800 mg/j | … | B-II |
| Fluconazole | | … | B-II |
| Induction therapy:[a] liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day) | Tr Org avec méningite | 2 weeks | B-III |
| AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day) | VIH Nég avec méningite | ≥4 weeks[a,b] | B-II |
| AmBd (0.7–1.0 mg/kg per day)[c] | | ≥6 weeks[a,b] | B-II |
| Immunosuppressed patients[a] and immunocompetent patients with severe pulmonary cryptococcosis | Same as CNS disease | 12 months | B-III |

66. For cryptococcemia or dissemination (involvement of at least 2 noncontiguous sites or evidence of high fungal burden based on cryptococcal antigen titer ⩾1:512), treat as CNS disease (B-III).

# Infections à Mucorales

# Polyenes et echinocandines

- Retrospective, two centres 1994–2006
- Mucormycosis sinus, orbit
  - 41 cases, 83% have diabet
- Treatment:
  - AmB: n=15
  - ABLC (5 mg/kg/d): n=22; r
  - L-AmB (5 mg/kg/d): n=4; r
- Success: 54%
  - Monotherapy: 45%
  - Bitherapy: 100%

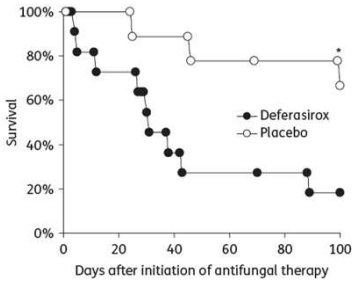



Reed C et al. *Clin Infect Dis* 2008;47:364–371.

ABLC: amphotericin B lipid complex; AmB: amphotericin B; CAS: caspofungin; CNS: central nervous system; L-AmB: liposomal AmB.

# Polyène et deferasirox

- Defeat study: L-AmB +/- deferasirox
- Multicentric randomised versus placebo, double blind
- Stratification: haemopoietic stem cell/ solid organ transplant?
- Treatment:
  - L-AmB ≥5 mg/kg/d
  - Deferasirox 20 mg/kg/d for 14 d




| | Deferasirox (N=11) | Placebo (N=9) |
|---|---|---|
| Active malignancy n (%) | 7 (64) | 3 (33) |
| Neutropoenia n (%) | 4 (36) | 1 (11) |
| L-AmB median dose (mg/kg) | 7.5 | 8 EB1 |
| Study medication duration (d) | 4 | 14 |

Spellberg B et al. *J Antimicrob Chemother* 2012;67:715–722.

L-AmB: liposomal amphotericin B

**Diapositive 36**

**EB1** This originally said 7; however on checking the paper the figure was 8 - we have therefore updated this but please do let us know if you would prefer the number to be changed back to 7.
Emma Beagley; 27/10/2014

# Polyène et posaconazole

- 32 patients with mucormycosis between 2007 and 2012
- Treated with L-AmB and posaconazole
- Identified in two large registries: SEIFEM and Fungiscope
- 29 patients (91%): second-line or third-line treatment
- 27 patients (93%): posaconazole as an addition to ongoing treatment with L-AmB
- Month 3: 59% mortality

Pagano L et al. *Haematologica* 2013;98:e127–e130.

L-AmB: liposomal amphotericin B

# Recommendations for first-line treatment of mucormycosis

ECIL3

| Intervention | SoR | QoR |
|---|---|---|
| Antifungal therapy, control of underlying disease and surgery | A | II |
| Antifungal therapy | | |
| Control of underlying condition | A | II |
| Surgery | | |
| Hyperbaric oxygen | C | III |

EFISG-ECMM

| Population | Intention | Intervention | SoR | QoR |
|---|---|---|---|---|
| Any | Increase survival | Surgical debridment | A | IIu |
| Any | Cure and increase survival | Surgical debridment in addition to antifungal treatment | A | IIu |
| Immuno-compromised | Increase survival | Immediate treatment initiation | A | IIu |

ECIL: European Conference on Infections in Leukemia; ECMM: European Confederation of Medical Mycology; EFISG: European Fungal Infection Study Group; QoR: quality of recommendation; SoR: strength of recommendation.

## Recommendations on targeted first-line antifungal treatment of mucormycosis in adult patients

EFISG-ECMM

| Population | Intention | Intervention | SoR | QoR |
|---|---|---|---|---|
| Any | Cure and increase survival | AmB, liposomal ≥5mg/kg | A | IIu |
| CNS | Cure | AmB, liposomal ≥10 mg/kg, initial 28 days | A | II |
| Any, except CNS | To cure | AmB, lipid complex ≥5mg/kg | B | IIu |
| Any | To cure | Posaconazole 200 mg X 4/d | B | IIu |
| Any | To cure | Lipid-based AmB + caspofungin | C | III |
| Any | To cure | AmB deoxycholate | D | I |

Treatment duration is determined on a case-by-case basis and depends on extent of surgery and organs involved

AmB: amphotericin B; ECCM: European Confederation of Medical Mycology; EFISG: European Fungal Infection Study Group; QoR: quality of recommendation; SoR: strength of recommendation.

## Recommendations on first-line antifungal treatment of mucormycosis

ECIL6

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

| | Grade | Comments |
|---|---|---|
| Management includes antifungal therapy, surgery and control of underlying conditions | A II | Multidisciplinary approach is required |
| Antifungal therapy | | |
| Amphotericin B deoxycholate | C II | |
| Liposomal amphotericin B | B II | Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure |
| Amphotericin B lipid complex | B II | |
| Amphotericin B colloidal dispersion | C II | |
| Posaconazole | C III | No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated. |
| Combination therapy | C III | |
| Control of underlying condition | A II | Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy |
| Surgery | | |
| Rhino-orbito-cerebral infection | A II | |
| Soft tissue infection | A II | |
| Localized pulmonary lesion | B III | |
| Disseminated infection | C III | Surgery should be considered on a case by case basis, using a multi-disciplinary approach |
| Hyperbaric oxygen | C III | |
| Recommendation against use | | |
| Combination with deferasirox | A II | |

CNS: central nervous system.

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ABCD: amphotericin B colloidal dispersion; ABLC: amphotericin B lipid complex; AmB: amphotericin B; CNS: central nervous system; L-AmB: liposomal amphotericin B; QoR: quality of recommendation; SoR: strength of recommendation.

# Recommendations on first-line antifungal treatment of mucormycosis

Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

| | Grade | Comments |
|---|---|---|
| Salvage therapy | | |
| Management includes antifungal therapy, control of underlying disease and surgery | A II | |
| Posaconazole | B II | |
| Combination of lipid amphotericin B and caspofungin | B III | |
| Combination of lipid amphotericin B and posaconazole | B III | |
| Maintenance therapy | | |
| Posaconazole | B III | Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a] |

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# Recommendations on first-line antifungal treatment of mucormycosis

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

Isavuconazole en cas d'intolérance ou d'échec de l'amphotéricine B liposomale

Place du posaconazole comprimé et IV?

ECIL6

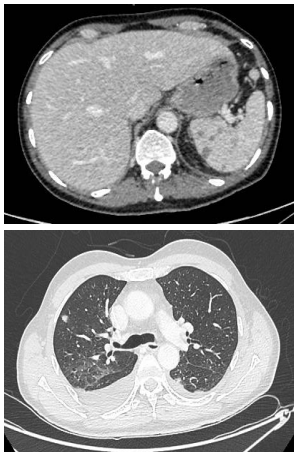
| | | |
|---|---|---|
| Combination therapy | C III | |
| Control of underlying condition | A II | Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy |
| Surgery | | |
| Rhino-orbito-cerebral infection | A II | |
| Soft tissue infection | A II | |
| Localized pulmonary lesion | B III | |
| Disseminated infection | C III | Surgery should be considered on a case by case basis, using a multi-disciplinary approach |
| Hyperbaric oxygen | C III | |
| Recommendation against use | | |
| Combination with deferasirox | A II | |

CNS: central nervous system.

ABCD: amphotericin B colloidal dispersion; ABLC: amphotericin B lipid complex; AmB: amphotericin B; CNS: central nervous system; L-AmB: liposomal amphotericin B; QoR: quality of recommendation; SoR: strength of recommendation.

## Scedosporiose

- Homme 42 ans
- 10 jours induction leucémie aigue myéloide
- Fièvre
- *Lomentospora prolificans*
- Voriconazole et terbinafine, transfusion de GB



# Associations antifongiques

- **En première ligne:**
  - Candida: bithérapie si site particulier
  - Cryptococcose neuro-méningée ou disséminée: toujours bithérapie
  - Aspergillose: pas de bithérapie en première ligne sauf cas sélectionnés
  - Mucormycose: pas de bithérapie en première ligne
  - Scedosporiose à *Lomentospora prolificans*: Voriconazole et terbinafine
- **En deuxième ligne:**
  - En cas d'échec de la monothérapie pour les infections à champignons filamenteux