

# INFECTIONS FONGIQUES

## TRAITEMENTS ANTIFONGIQUES

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# Molécules disponibles

- **Polyènes**
  - Ampho B déoxycholate
  - Ampho B liposomale
- **Azols**
  - Fluconazole
  - Voriconazole
  - Itraconazole
  - Posaconazole
- **Echinocandines**
  - Caspofungine
  - Micafungine
  - Anidulafungine
- **Flucytosine (5-FC)**

# Guidelines

- SPILF:
  - ▣ Prothèse: RPC 2008, recommandations précises
  - ▣ Spondylodiscite: RPC 2007, recommandations précises
  
- ESCMID:
  - ▣ ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. O.A.Cornely, CMI 2012.
  
- IDSA:
  - ▣ Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the IDSA. P.G. Pappas, CID 2009.
  - ▣ Treatment of Aspergillosis: Clinical Practice Guidelines of the IDSA. T.J. Walsh, CID 2008.

# Guidelines

## □ Candida

### □ Arthrite

- Chirurgie de lavage/Ablation du matériel (A3)

- FCZ ou L-AmB ou Echinocandine 2 sem puis FCZ 4 sem min (B3).

- L-AmB 2 semaines +/- 5-FC puis FCZ 3 à 6 mois.

### □ Ostéomyélite/spondylodiscite: 6-12 mois

## □ Aspergillus

### □ Arthrite/Osteomyélite

- Chirurgie de lavage/Ablation du matériel (B3)

- Voriconazole ou L-AmB (B2) 6 à 8 sem minimum

- Voriconazole ou L-AmB 6 mois.

# Guidelines

## Evidence Summary

Approaches to osteoarticular infections are based on anecdotal case reports and open-label series. The published experience is heavily dominated by reports of use of AmB-d, fluconazole, and more recently, caspofungin. Use of LFAmB, other azoles, and other echinocandins would appear to be reasonable, but experience is limited.

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the IDSA. P.G. Pappas, CID 2009.

# Quelle molécule?

	Administrati on	Posologie	Asp/Candida
<b>Polyènes</b>			
Ampho B déoxycholate	IV	0,5-1 mg/kg/j	Cide/Cide
Ampho B liposomale	IV	3-5 mg/kg/J	Cide/Cide
<b>Azolés</b>			
Fluconazole	IV/PO	6 mg/kg/j	0/Static
Voriconazole	IV/PO	200 mg/j	Cide/Static
Itraconazole	IV/PO	200 mg/j	Cide/Static
Posaconazole	IV/PO	200 mgx4/j	Cide/Static
<b>Echinocandines</b>			
Caspofungine	IV	70-50 mg/j	Static/Cide
Micafungine	IV	100 mg/j	Static/Cide
Anidulafungine	IV	100 mg/j	Static/Cide
<b>Flucytosine (5-FC)</b>	IV/PO	150 mg/kg/j	0/Static

# Pénétration tissulaire

Tissue Penetration of Antifungal Agents. T Felton, Clinical Microbiology Reviews 2014.

- ▣ Polyènes
- ▣ Azolés
  - ▣ Voriconazole > Itraconazole > Fluconazole
- ▣ Echinocandines
- ▣ Flucytosine

	C Os/ C Plasma
	<0,5
	0,5-5
	>5

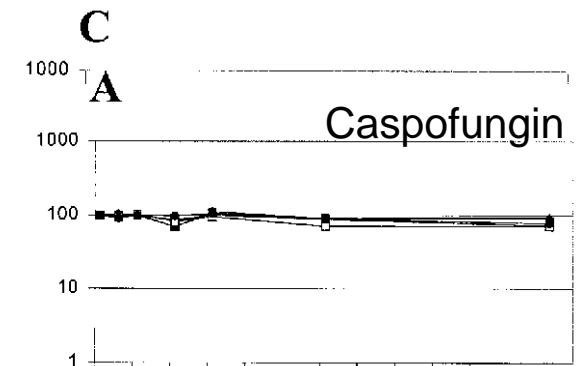
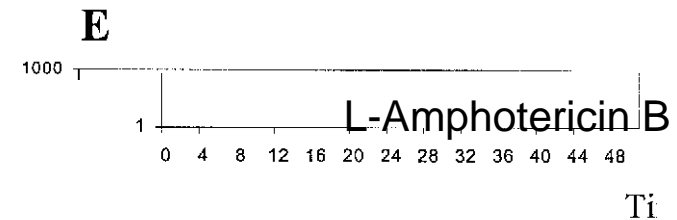
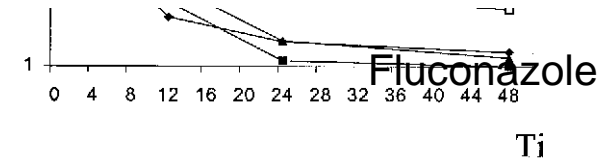
Compound	Bone	
	Tissue	Synovial fluid
Fluconazole	X ○	X
Itraconazole	X	X
Voriconazole	X	X
Posaconazole		
AmBd	○	X
ABLC	○	
L-AMB	○	
5-FC	○	○
Anidulafungin	○	
Caspofungin		
Micafungin		

# Biofilm et candida in vitro

TABLE 1. MICs of antifungal agents against planktonic and biofilm-associated *C. albicans* (M61 and GDH) and *C. parapsilosis* (P/A71 and P92) strains<sup>a</sup>

Drug	MIC ( $\mu\text{g/ml}$ ) in:							
	Planktonically grown cells for strain:				Biofilm at 48 h for strain:			
	M61	GDH	P/A71	P92	M61	GDH	P/A71	P92
AMB	0.5	0.25	0.25	0.5	4	4	8	8
NYT	2	1	0.5	2	16	16	16	64
Chlor	8	8	8	8	32	8	16	64
TRB	32	32	4	1	128	128	*	128
FLC	1	0.25	8	1	>256	>256	>256	>256
VRC	0.5	8	0.125	0.03	>256	>256	128	256
Ravu	0.1	0.06	0.125	0.1	128	128	*	128
Lip-AMB	0.5	0.06	0.06	0.5	0.25	0.25	1	*
Lip-NYT	0.5	0.06	0.5	0.5	8	16	32	*
ABLC	0.25	0.06	0.06	0.25	0.25	0.25	0.25	*
Casp	0.125	0.125	1	1	0.25	0.5	0.125	4
Mica	0.001	0.001	0.25	0.5	0.25	0.5	0.125	2

Log plots of killing kinetics of fluconazole, amphotericin B and caspofungin against preformed biofilms of *C. albicans*



In Vitro Pharmacodynamic Properties of 3 Antifungal Agents against Preformed *Candida albicans* Biofilms Determined by Time-Kill Studies. Gordon Ramage. AAC

Antifungal Susceptibility of *Candida* Biofilms: Unique Efficacy of Amphotericin B Lipid Formulations and Echinocandins. D. M. Kuhn. AAC 2002.



# Etudes cliniques

## Candida

### Candida osteomyelitis: Analysis of 207 Pediatric and Adult Cases (1970–2011) M.N. Gamaletsou, CID 2012.

#### No. of bones infected per patient

1	34 (16)
2	98 (47)
≥3	75 (36)

#### Type of bone infected

Vertebra <sup>a</sup>	105 (51)
Femur	30 (14)
Rib	27 (13)
Sternum	23 (11)
Humerus	17 (8)
Tibia	16 (8)

#### Concomitant joint involvement

Intervertebral joint	82 (40)
Costochondral/costosternal joint	22 (11)
Synovial joint	43 (21)
Knee	22 (11)
Hip	10 (5)
Ankle	7 (3)

#### Candida spp

<i>C. albicans</i>	134 (65)
<i>C. tropicalis</i>	33 (16)
<i>C. glabrata</i>	17 (8)
<i>C. parapsilosis</i>	14 (7)
<i>C. krusei</i>	2 (1)
<i>C. guilliermondii</i>	2 (1)
Not specified	13 (6)
Other <sup>c</sup>	5 (2)

# Etudes cliniques

## Candida

### Candida osteomyelitis: Analysis of 207 Pediatric and Adult Cases (1970–2011) M.N. Gamaletsou, CID 2012.

Therapeutic Intervention <sup>a</sup>	No. (%)	Favorable Response (Complete Response + Partial Response), No. (%)	Failure, No. (%)	Relapse, No. (%) <sup>b</sup>
Only antifungal agents	92 (44)	89 (97)	3 (3)	16 (17)
Only surgery <sup>c</sup>	10 (5)	8 (80)	1 (10)	2 (20)
Antifungal agents and surgery	100 (48)	90 (90)	10 (10)	43 (43)
Class of antifungal agent(s) used; median duration of treatment (range)				
Polyenes <sup>d</sup> ; 42 days (range, 9–360 days)	46 (22)	40 (87)	6 (13)	12 (26)
Azoles <sup>d</sup> ; 330 days (range, 42–480 days)	42 (20)	39 (93)	3 (7)	12 (29)
Flucytosine <sup>d</sup> ; 42 days (range, 33–97 days)	8 (4)	8 (100)	0 (0)	2 (25)
Echinocandin; 7 days (range, 7 days)	1 (0.5)	1 (100)	0 (0)	1 (100)
Combination <sup>e</sup> ; 200 days (range, 19–540 days)	94 (45)	90 (96)	4 (4)	32 (34)

#### Total outcome

Median duration of therapy, 90 days (range, 7–720 days)

Complete response, 90 days (range, 19–540 days)	<u>66 (32)</u> ; 32% relapsed)
Partial response, 90 days (range, 7–720 days)	123 (59; 27% relapsed)
Failure, 42 days (range, 9–480 days)	15 (7)
Lost to follow-up	3 (1)

**Infection sur matériel: 11 patients**  
**Réponse complète 3 (27%)**  
**Réponse partielle 7 (64%)**  
**Rechute 5 (45%) , Décès 1 (9%)**

# Etudes cliniques

## Candida

2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections. An analysis of 164 patients, 156 from the literature and 8 own cases. J.WP Kuiper. *Acta Orthopaedica* 2013.

- Traitement administré:
  - amphotericine B (71 patients)
  - fluconazole (80 patients)
  - echinocandine, 6 patients (2005–2012): caspo (3), mica (2), anidula (1).
- Durée moyenne de traitement: 3.8 (0–36) mois.
  - 0-6 semaines: 13 patients
  - 0-2 mois: 28 patients
  - 0-3 mois: 40 patients
  - 0-6 mois: 48 patients

Meilleure réponse chez les patients ayant un ttt court.

# Etudes cliniques

## Aspergillus

- Aspergillus Vertebral Osteomyelitis in Immunocompetent Hosts: Role of Triazole Antifungal Therapy. Alex Studemeister<sup>1,2,3</sup> and David A. Stevens. CID 2011.
- Aspergillus vertebral osteomyelitis in immunocompetent subjects: case report and review of the literature. A. Nicolle, Infection 2012.
- « Bon » pronostic: 70-75% de guérison
  - Chirurgie
  - Voriconazole ≥ L Ampho B

# Prise et surveillance du traitement

	Toxicité	Interaction	Dosage	Prise
<b>Polyènes</b>				
Ampho B	Rein ++			
L-Ampho B	Rein			
<b>Azols</b>				
Fluconazole	Foie	++		
Voriconazole	Foie ophtalmo	++	0,8-2,5 mg/L	A jeun
Itraconazole	Foie	++	>0,5 mg/l	
Posaconazole	Foie	++	>1,2 mg/L	Repas gras
<b>Echinocandines</b>				
Caspofungine		Tacro, ARV		
Micafungine				
Anidulafungine				
<b>Flucytosine</b>	Hémato		50-100mg/L	

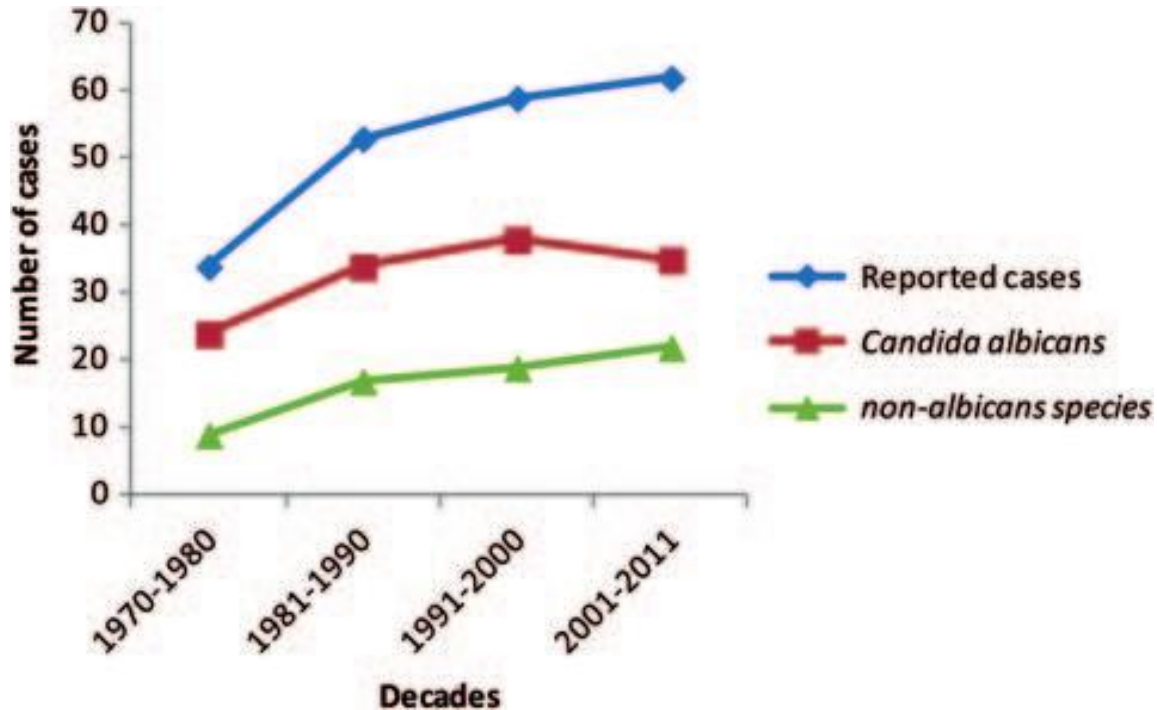
# Conclusion

- Pathologie rare
- Faiblesse des preuves scientifiques
- Suivi du traitement
- Guidelines toujours valables.
  
- Reste à préciser/développer:
  - ▣ Cohorte de suivi prospectif
  - ▣ Echinocandines
  - ▣ Durée de traitement
  - ▣ Place des associations
  - ▣ Molécule anti biofilm
  - ...

MERCI DE VOTRE  
ATTENTION



# Epidémiologie

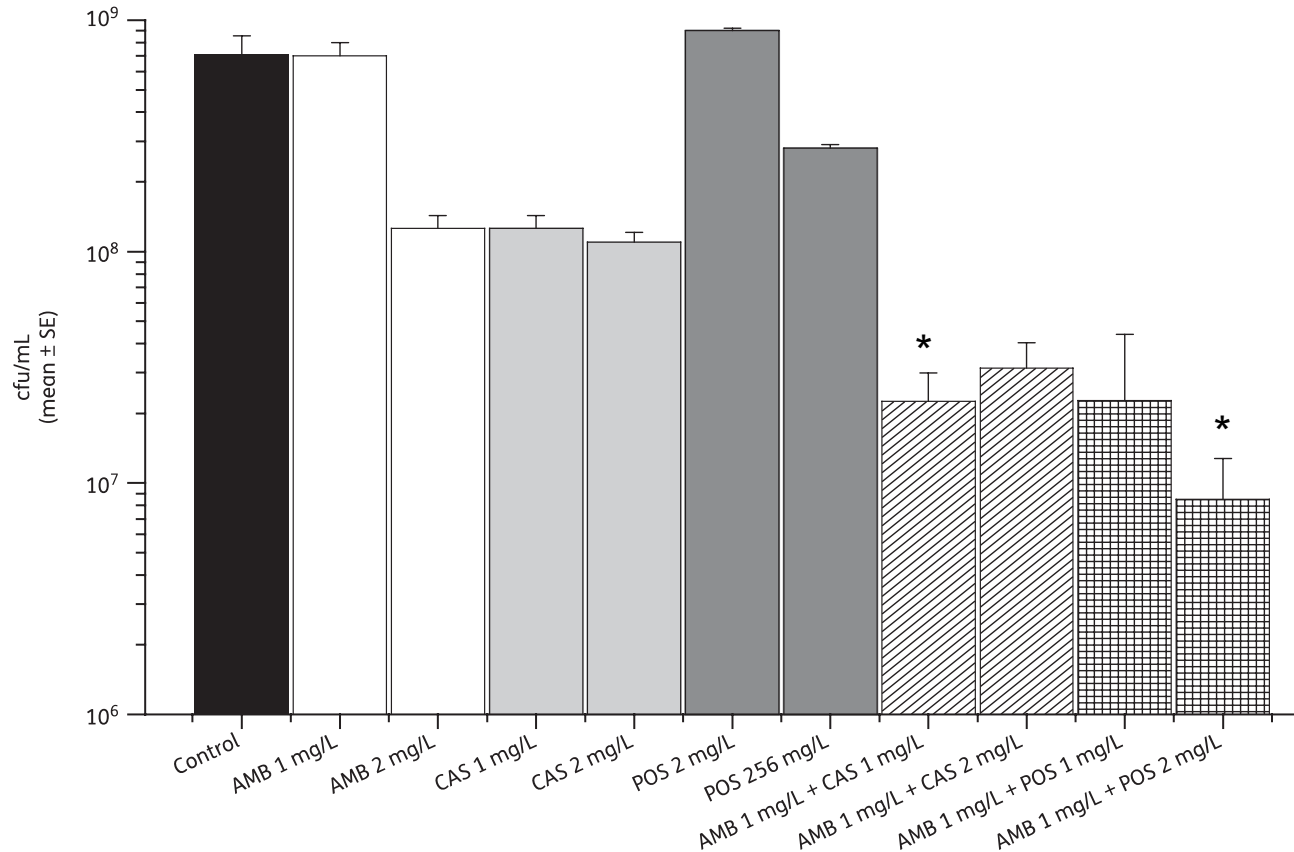


**Figure 1.** Number of reported cases of *Candida* osteomyelitis per decade, 1970–2011.





# Biofilm et candida in vitro associations



**Figure 1.** Reduction of the fungal colony counts (cfu/mL) in the biofilms of 10 invasive *C. albicans* isolates after incubation with amphotericin B (AMB), caspofungin (CAS) and posaconazole (POS) alone or in combination. The concentrations of antifungal drugs alone or in combination are in accordance with the MICs determined using the XTT assay.

# Etudes cliniques

## Candida

Treatment and outcomes of *Candida* osteomyelitis: review of 53 cases from the PATH Alliance® registry. D. Neofytos. EJCMI 2014.

**Table 2** Antifungal therapy for 36 patients with *Candida* osteomyelitis who were treated with a single agent

	All	<i>C. albicans</i>	<i>C. parapsilosis</i>	<i>C. glabrata</i>	<i>C. tropicalis</i>
Number of patients, <i>n</i>	36	22 <sup>a,b</sup>	7	6 <sup>b</sup>	2
Fluconazole	25	19 <sup>a</sup>	5	0	1
Voriconazole	1 <sup>b</sup>	1	0	1	0
<u>Echinocandins<sup>c</sup></u>	9	2	2	4	1
Amphotericin B	1	0	0	1	0

# Molécules disponibles

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