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Systemic mycosis: treatment and prevention

Maria Nina Chitasombat M.D.
Assistant Professor
Infectious disease division
Department of Internal Medicine
Faculty of Medicine, Ramathibodi Hospital
Mahidol University

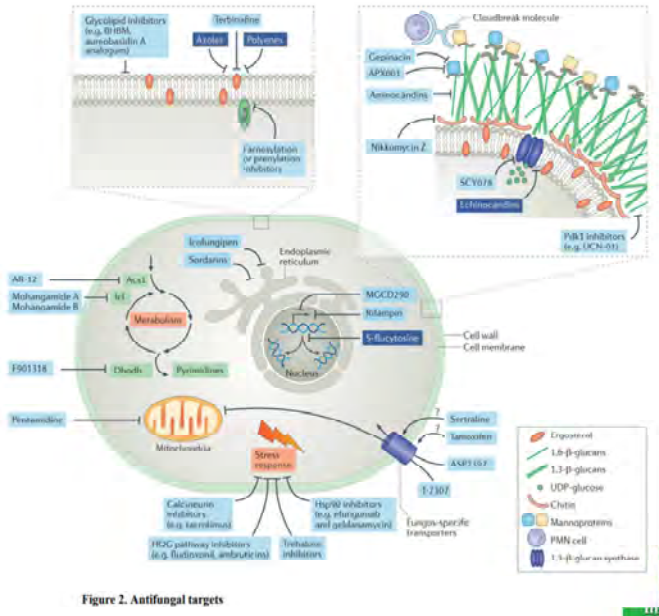

Figure 2. Antifungal targets

Perfect JR. *Nat Rev Drug Discov* 2017;16:603-616.

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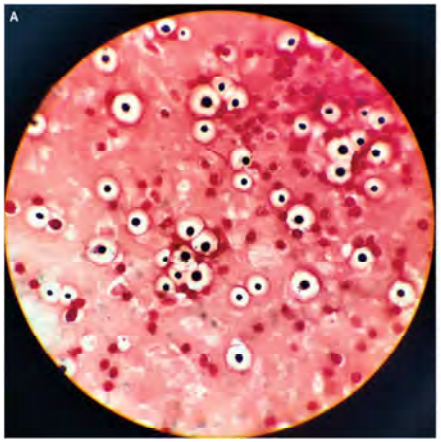
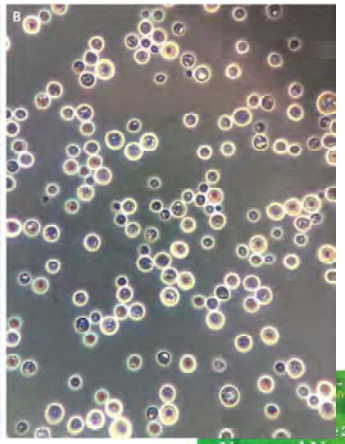
Cryptococcosis

Cryptococcus spp. are encapsulated, polysaccharide-coated yeasts with two major species (*C. neoformans* and *C. gattii*)





N Engl J Med 2018;379:1281

Treatment of Cryptococcosis in AIDS pt

IDSA GUIDELINE

Cryptococcocal Meningitis

- Patients with severe pulmonary disease
- Patients with disseminated disease (at least two noncontiguous sites)
- Patients with serum cryptococcal antigen titer ≥1:512

-> Should be managed as for CNS disease, even normal CSF findings (high fungal burden)

- Patients with serum cryptococcal antigenemia

-> should have LP performed

-> if normal CSF findings including CSF cryptococcal antigen, should start fluconazole treatment (consolidation phase) and ART initiation

Perfect JR. et al. CID 2010; 50(3):291-322
Pappas PG. et al. CID 2009; 48(12):1775-83

IDSA GUIDELINE

Cryptococcocal Meningitis in non-HIV Patient

Clinical course more severe disease than AIDS patient

Antifungal Treatment	Transplant	Non-HIV/transplant
Induction phase*	Duration of treatment	
Liposomal AmB (3–4 mg/kg/d) +flucytosine	2 weeks	2-4 weeks
Liposomal AmB (3–4 mg/kg/d)	4-6 weeks	≥4 weeks
Amphotericin B deoxycholate (0.7-1 mg/kg/day)	4-6 weeks	≥6 weeks
	Varies depend on clinical response, CSF sterilization	
Consolidation phase Fluconazole 400-800 mg/day	8 weeks	8 weeks
Maintenance phase Fluconazole 200-400 mg/day	6-12 months	6-12 months

Perfect JR. et al. CID 2010; 50(3):291-322.

IDSA GUIDELINE

Adverse Reactions of Antifungals

Amphotericin B deoxycholate	Flucytosine	Fluconazole
Infusion reactions e.g. fever, chills (required premeds with CPM and paracetamol)	Bone marrow suppression (anemia, neutropenia)	Hepatoxicity (avoid use of concomitant hepatotoxic drug)
-Electrolyte imbalance e.g. hypoK, hypoMg -Nephrotoxicity (required iv. premed NSS 0.5-1 L in 2 h)*	Hepatoxicity	Drug interactions (inhibitor of CYP450 isozyme CYP2C19 (CYP3A4 and CYP2C9 to lesser extent)

Liposomal AmB (better CNS penetration, higher cost)

Perfect JR. et al. CID 2010; 50(3):291-322.

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ACTA Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

S.F. Molloy, C. Kanyama, R.S. Heyderman, A. Loyse, C. Kouanfack, D. Chanda, S. Mfinanga, E. Temfack, S. Lakhi, S. Lesikari, A.K. Chan, N. Stone, N. Kalata, N. Karunaharan, K. Gaskell, M. Peirse, J. Ellis, C. Chawinga, S. Lontsi, J.-G. Ndong, P. Bright, D. Lupiya, T. Chen, J. Bradley, J. Adams, C. van der Horst, J.J. van Oosterhout, V. Sini, Y.N. Mapoure, P. Mwaba, T. Bicanic, D.G. Lalloo, D. Wang, M.C. Hosseinipour, O. Lortholary, S. Jaffar, and T.S. Harrison, for the ACTA Trial Study Team*

N Engl J Med 2018;378:1004-17.

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ACTA Trial

Open-label, phase 3, randomized, noninferiority, multicenter trial (Advancing Cryptococcal Meningitis Treatment for Africa)

PO	IV	IV
Fluconazole plus flucytosine	1 week of amphotericin B (1 MKD)	2 weeks of amphotericin B (1 MKD)
Fluconazole(1200 mg per day) plus flucytosine (100 MKD) given orally for 2 weeks.	plus either fluconazole (1200 mg per day) **or** flucytosine (100 MKD) for 7 days, **followed** on days 8 through 14 by fluconazole (1200 mg per day).	plus either fluconazole (1200 mg per day) **or** flucytosine (100 MKD) for 14 days.

LP D0, 7, 14 or daily if high ICP
After 2 weeks, fluconazole was given at 800 mg per day until ART was started at 4 weeks at 400 mg per day until 10 weeks, and at 200 mg per day thereafter

N Engl J Med 2018;378:1004-17.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Oral Regimen (N=225)	1-Wk Amphotericin B (N=224)	2-Wk Amphotericin B (N=229)
Male sex — no. (%)	119 (52.9)	137 (61.2)	134 (58.5)
Median age (IQR) — yr	36.0 (32.0–43.0)	38.5 (32.0–44.0)	37.0 (32.0–43.0)
Reported ART exposure — no. (%)†	128 (56.9)	119 (53.1)	134 (58.5)
Median weight (IQR) — kg‡	50 (46–60)	53 (47–60)	51 (46–60)
Median CSF fungal count (IQR) — $\log_{10}$ CFU/ml§§	5.0 (3.7–5.7)	5.0 (3.5–5.9)	5.0 (3.8–5.7)
Median CSF opening pressure (IQR) — cm††	22 (13–35)	24 (13–38)	25 (15–38)
CSF opening pressure >30 cm — no./total no. (%)‡‡	69/218 (31.7)	78/211 (37.0)	80/215 (37.2)
Median CSF white-cell count (IQR) — cells/mm^3§§	4.0 (0.0–20.0)	4.0 (0.0–15.0)	3.0 (0.0–15.0)
Median CSF glucose level (IQR) — mmol/liter‖‖	2.0 (1.0–2.6)	2.0 (1.0–2.6)	2.0 (1.0–2.4)
Median CSF protein level (IQR) — mg/dl¶¶	113 (48–190)	102 (5–163)	99 (55–154)
Median hemoglobin level (IQR) — g/dl‖‖	10.7 (9.2–12.1)	11.0 (10.0–12.5)	10.9 (9.6–12.4)
Median creatinine level (IQR) — mg/dl***	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.7 (0.6–0.9)
Median baseline CD4+ cell count (IQR) — cells/mm^3†††	25 (10–63)	26.5 (12–63)	26 (10–64)

N Engl J Med 2018;378:1004-17

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Table 3. Unadjusted Time-to-Event Analysis of Mortality and Rate of Fungal Clearance in CSF According to Partner Treatment with Amphotericin B in the Intention-to-Treat Population.*

Outcome	Amphotericin B + Fluconazole (N=225)	Amphotericin B + Flucytosine (N=228)	Hazard Ratio (95% CI)	P Value†
Mortality at 10 wk				
No. of deaths	101	71		
% (95% CI)	45.0 (38.5 to 51.5)	31.1 (25.3 to 37.3)	0.62 (0.45 to 0.84)	0.002
Mortality at 2 wk				
No. of deaths	61	37		
% (95% CI)	27.1 (21.3 to 32.9)	16.3 (11.5 to 21.1)	0.56 (0.37 to 0.85)	0.006
Mortality at 4 wk				
No. of deaths	86	57		
% (95% CI)	38.2 (31.9 to 44.6)	25.1 (19.4 to 30.7)	0.59 (0.42 to 0.83)	0.002
			Difference in Mean Clearance Rate (95% CI)	
Fungal clearance†				
No. of patients	175	186		
Clearance rate — $\log_{10}$ CFU/ml/day	−0.36±0.23	−0.46±0.25	−0.06 (−0.03 to −0.08)	<0.001

N Engl J Med 2018;378:1004-17

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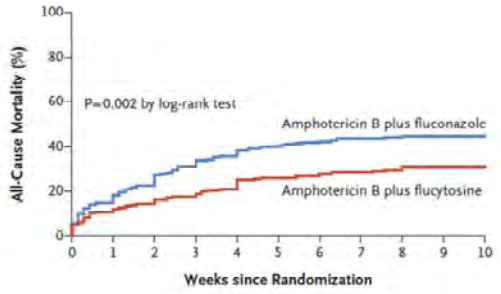
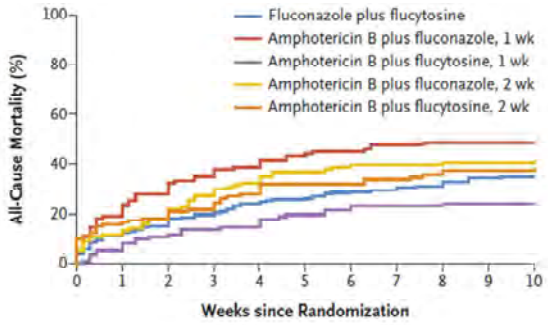
B



No. at Risk											
Amphotericin B plus fluconazole	225	191	174	155	145	135	130	126	125	124	122
Amphotericin B plus flucytosine	228	203	194	187	179	167	165	161	159	156	153

N Engl J Med 2018;378:1004-17

C



No. at Risk											
Fluconazole plus flucytosine	225	200	192	181	171	167	161	159	155	147	144
Amphotericin B plus fluconazole, 1 wk	111	90	80	72	68	63	61	58	57	57	57
Amphotericin B plus flucytosine, 1 wk	113	106	100	97	96	89	87	85	85	84	82
Amphotericin B plus fluconazole, 2 wk	114	101	94	83	77	72	69	68	68	67	65
Amphotericin B plus flucytosine, 2 wk	115	97	94	90	83	78	78	76	74	72	71

N Engl J Med 2018;378:1004-17

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- One week of amphotericin B plus flucytosine was associated with the lowest 10-week mortality (24.2%; 95% CI, 16.2 to 32.1)
- **1-week amphotericin B–flucytosine group was significantly lower than that in the other amphotericin B groups, whereas mortality in the 1-week amphotericin B–fluconazole group was the highest.**
- Side effects, such as severe anemia, were more frequent with 2 weeks than with 1 week of amphotericin B or with the oral regimen

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Table 5. Laboratory-Defined and Clinical Adverse Events That Occurred within 21 Days after Randomization, According to Treatment Strategy.*

Event	Oral Regimen (N=225)	1-Wk Amphotericin B (N=224)	2-Wk Amphotericin B (N=228)
Any adverse event — no. of patients (%)			
Grade 3 or 4†	129 (57.3)	128 (57.1)	154 (67.5)
Grade 3	60 (26.7)	60 (26.8)	74 (32.5)
Grade 4	69 (30.7)	68 (30.4)	80 (35.1)
Anemia — no. of patients (%)			
Grade 3‡	9 (4.0)	20 (8.9)	40 (17.5)
Grade 4§	2 (0.9)	11 (4.9)	20 (8.8)
Elevated ALT — no. of patients (%)			
Grade 3‡	6 (2.7)	6 (2.7)	7 (3.1)
Grade 4§	0	1 (0.4)	1 (0.4)
Creatinine increase — no. of patients (%)			
Grade 3‡	6 (2.7)	13 (5.8)	16 (7.0)
Grade 4§	5 (2.2)	1 (0.4)	4 (1.8)
Median change in creatinine level to day 14 (IQR) — μmol per liter‖	0 (−8.8 to 13.0)	14.0 (0.0 to 33.0)	35.4 (12.0 to 65.0)

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Efficacy of Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis: an open-label dose-ranging study

- Sertraline is concentrated into brain tissue at a median of 16·5-fold higher levels than in plasma
- In vitro, sertraline inhibited C. neoformans growth with minimum inhibitory concentrations (MIC) between 2–6 mcg/mL;– and unlike fluconazole, sertraline was **fungicidal**, with killing independent of cell proliferation
- Therapeutic levels of sertraline in the brain should be achieved in 97% of persons when dosed at **400mg/day**, 90% of persons dosed at 200mg/day without ART
- Sertraline had faster cryptococcal CSF clearance, decreased IRIS, and decreased relapse compared with historical experiences

Lancet Infect Dis. 2016; 16(7): 809–818

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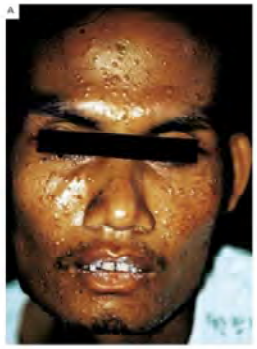
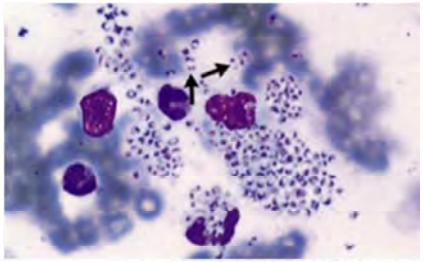
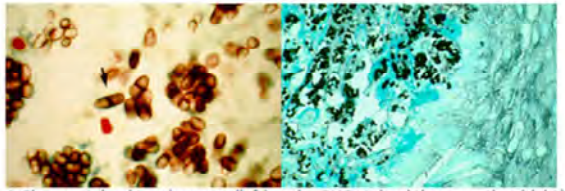
Penicilliosis

Talaromyces marneffei
(Penicillium marneffei)



Multiple umbilicated papule





A Giemsa stained touch smear (left) and a GMS stained tissue section (right)

Kenrad E. Nelson, M.D., and Thira Sirisanthana, M.D. N Engl J Med 2001; 344:1763