Case 5: Difficult-to-treat infections

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Disclosures

- The speaker declares no conflict of interest.

Background

- Cryptococcal infections are increasingly diagnosed in non-HIV non-transplant (NHNT) host
- Combination of L-AmB + 5FC has better early fungicidal activity as compared to other regimens
- Treatment related challenges are multifactorial
  - Financial
  - Availability (L-AmB and 5FC)
  - Drug related toxicities
  - Hospitalization and central line related infections
  - Diagnosis and management of raised intracranial pressure
  - Achieving sterile CSF in NHNT host
  - Requires prolonged induction therapy

Molloy SF, et al. *N Engl J Med* 2018;378:1004-17; Tenforde MW, et al. *J Int AIDS Soc 2020*;23(1):e25416. Beardsley J, J Fungi (Basel). 2019 Aug 2;5(3):71.

Case history

- 28/M, 75kg, residing in Gujarat state, previously healthy, rice mill worker
- Presented to neurologist with
  - Headache, tingling and numbness in right upper limb
- Work up at Neurology clinic:
  - CSF examination: Normal
  - MRI Brain (Contrast study), and MR Venogram: Normal
  - HIV, HBsAg, Biochemical tests were normal
- Prescribed pain killer and antidepressant without significant improvement

Case follow up

- Persistent symptoms
- Repeat CSF after 2 weeks of initial presentation
  - Proteins: 37.7 mg/dL,
  - Sugar: 41 mg/dL (RBS 110),
  - TC: 15/cmm, all lymphocytes, budding capsulated yeast cells seen on India Ink
- Patient was prescribed Tab Fluconazole 200 mg BID
- Follow-up CSF after 3 weeks of Rx
  - Protein: 56.7 mg/dL
  - Sugar: 41 mg/dL (124)
  - TC: 4/cmm
- Good clinical response
- Fluconazole cont'd. for 10 weeks

What is the best strategy to manage this situation?

a) I agree with current therapy as patient has responded

b) I agree with the current therapy but will use higher dose of fluconazole

c) I will manage this case with Amphotericin B induction followed by fluconazole consolidation and maintenance

d) I will manage this case with combination of Amphotericin B + 5FC induction followed by fluconazole consolidation and maintenance

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What is the best strategy to manage this situation?

ⓘ Start presenting to display the poll results on this slide.

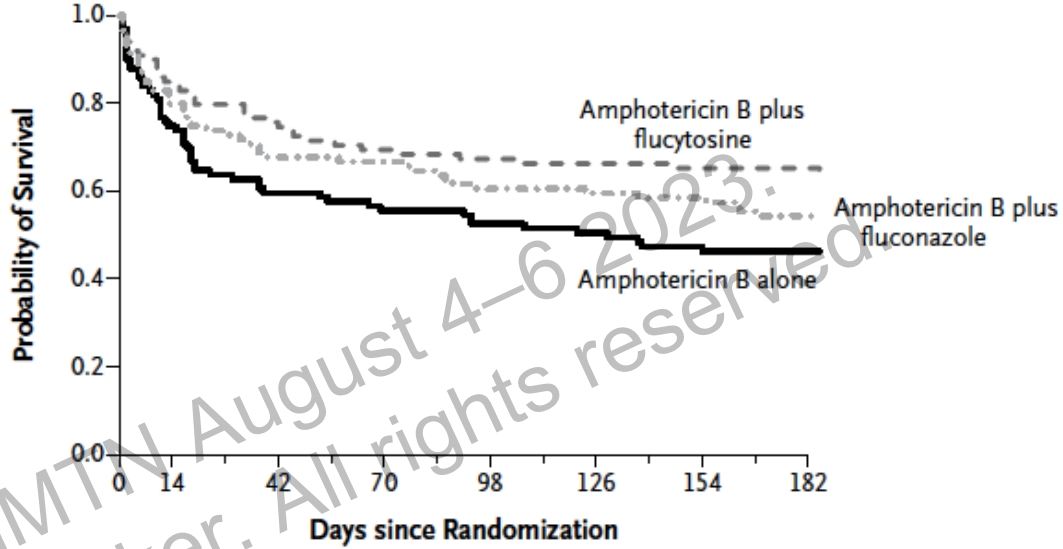
The NEW ENGLAND JOURNAL of MEDICINE

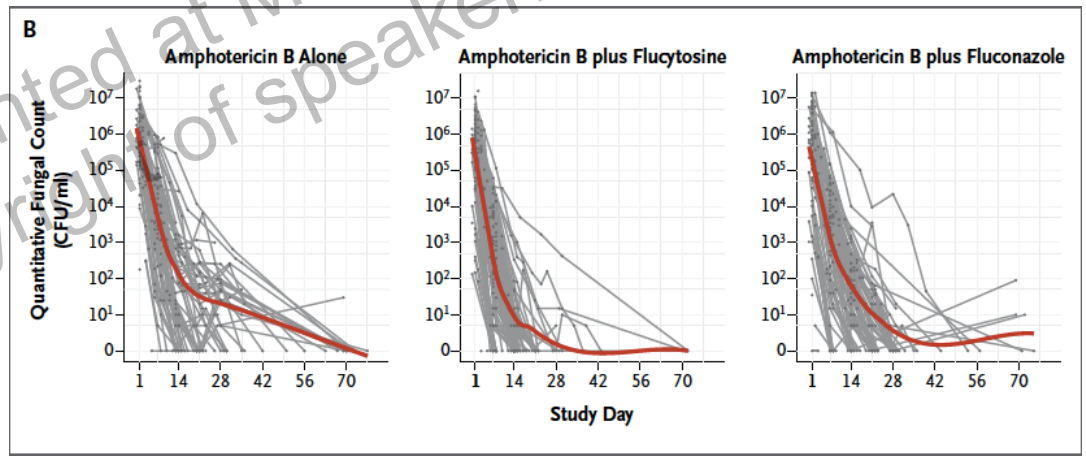
ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

Jeremy N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D., Pham P. Mai, M.D., Nguyen T. Dung, M.D., Nguyen H. Mai, M.D., Ph.D., Nguyen H. Phu, M.D., Ph.D., Ho D. Nghia, M.D., Ph.D., Nguyen D. Phong, M.D., Ph.D., Cao Q. Thai, M.D., Le H. Thai, M.D., Ly V. Chuong, M.D., Dinh X. Sinh, M.D., Van A. Duong, B.Sc., Thu N. Hoang, M.Sc., Pham T. Diep, B.Sc., James I. Campbell, M.I.B.M.S., Tran P.M. Sieu, M.D., Stephen G. Baker, Ph.D., Nguyen V.V. Chau, M.D., Ph.D., Tran T. Hien, M.D., Ph.D., David G. Lalloo, M.D., and Jeremy J. Farrar, M.D., D.Phil.

N Engl J Med 2013;368:1291-302





ORIGINAL ARTICLE

mycoses WILEY

Comparison of liposomal amphotericin B alone and in combination with flucytosine in the treatment of non-HIV *Cryptococcal* meningitis: A nationwide observational study

Takahiro Takazono[1,2] | Yusuke Hidaka[1,2,3] | Shimpei Morimoto[4,5] | Masato Tashiro[1,6] |

- L- AMB with 5-FC showed better prognosis than L-AMB (mortality 6% vs. 11%), No significant difference (HR, 0.5775; 95% CI, 0.2748–1.213; p = 0.1)
- Effect of adding 5-FC on the L-AMB treatment was smaller when the observation was extended to 30 days after diagnosis (mortality 12.4% vs. 15.1%, HR, 0.8285; 95% CI, 0.4667–1.471; p = 0.5)

Days	0	7	14	21	28	30
AMB	149	135	126	118	107	25
MB+5FC	217	216	207	193	180	39

Takazono T, *Mycoses*. 2022;65:897-902.

Which of the following is not required for the management of this patient?

a) Cryptococcal drug susceptibility testing
b) CSF CrAg titer, opening pressure, CSF lactate
c) Work up to rule out TB co-infection
d) Work up for immunodeficiency disorder

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Which of the following is not required for the management of this patient?

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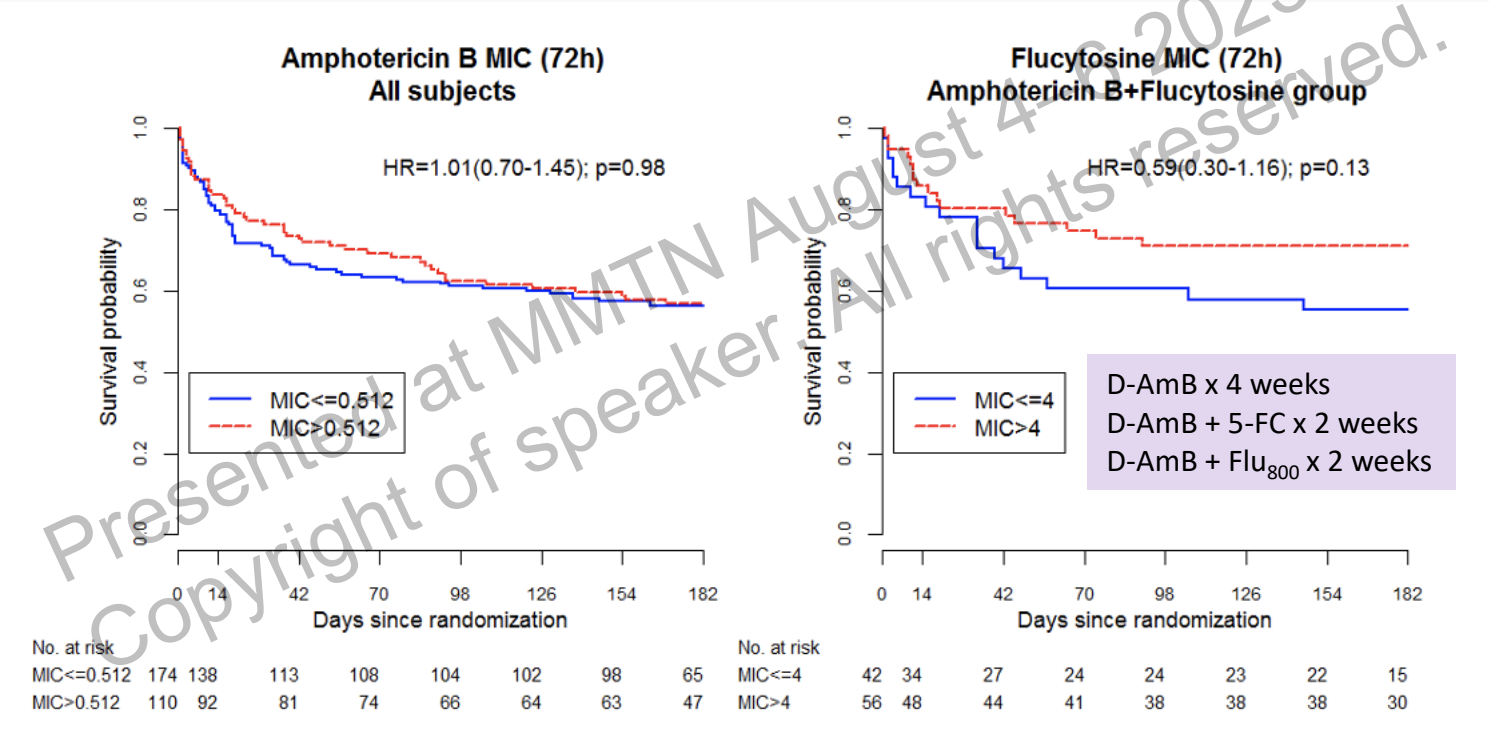
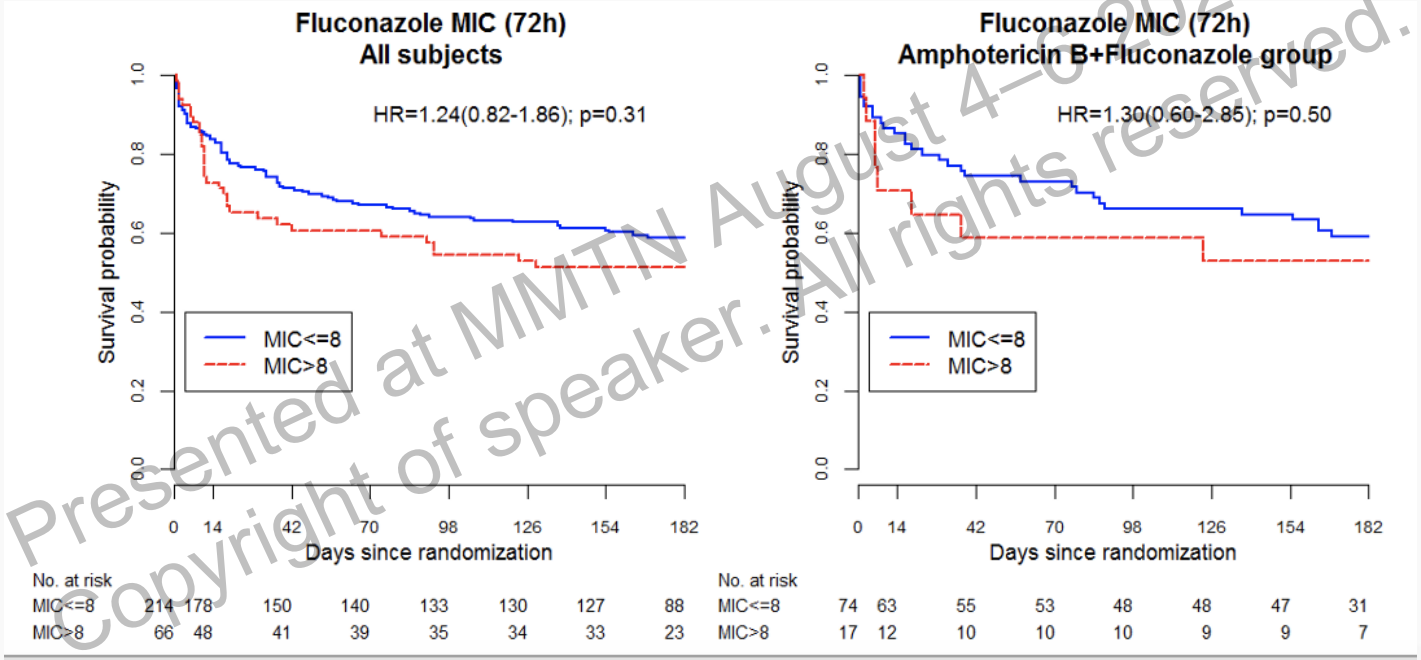
Baseline antifungal susceptibility in CM treatment

AST of baseline isolates of C. neoformans does not correlate with survival or mycological clearance



Connor LO, et al. Clin Infect Dis 2021;73:e2338–e2341

Antifungal susceptibility does not correlate with fungal clearance or survival in AIDS-associated cryptococcal meningitis



AST has no place in routine clinical use in first episodes of cryptococcal meningitis

Connor LO, et al. Clin Infect Dis 2021;73:e2338–e2341

Clinical Infectious Diseases
MAJOR ARTICLE

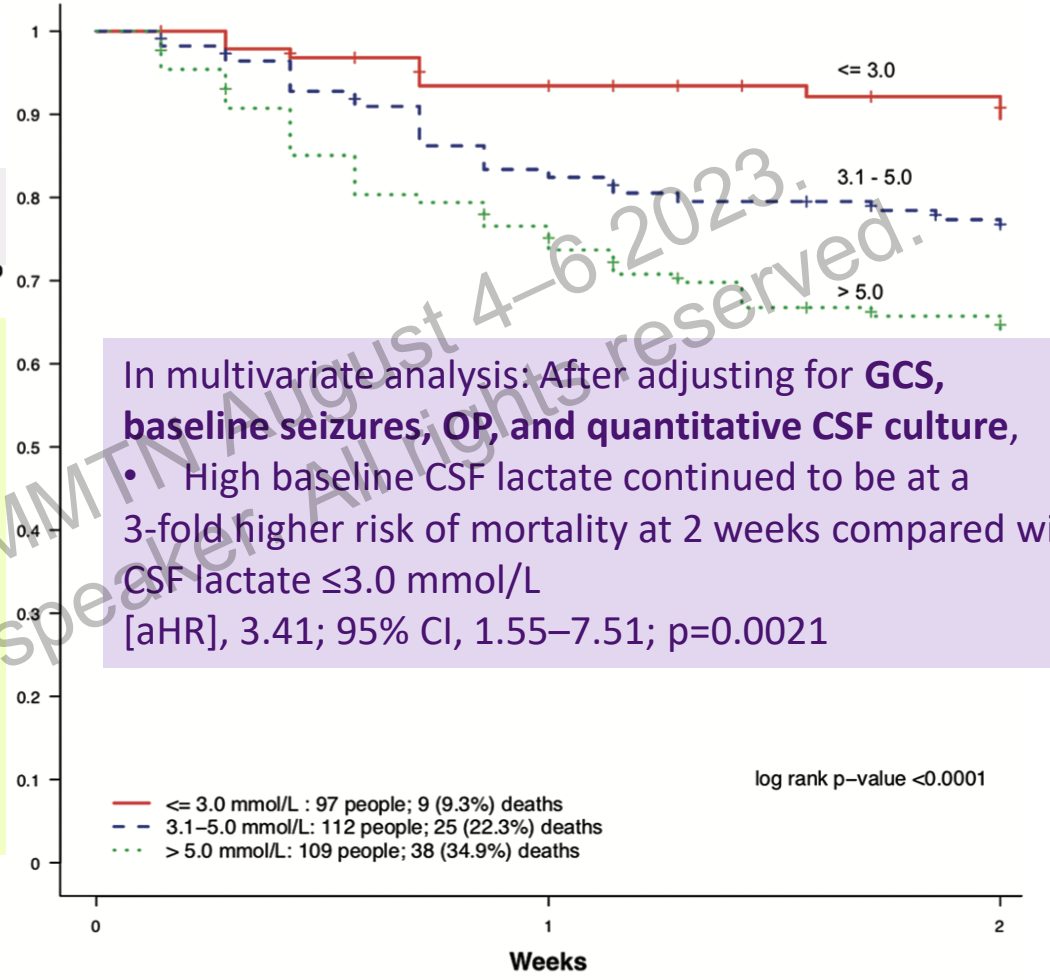
Cerebrospinal Fluid Lactate as a Prognostic Marker of Disease Severity and Mortality in Cryptococcal Meningitis

Mahsa Abassi,[1,2] Ananta S. Bangdiwala,[2] Edwin Nuwagira,[3] Kiiza Kandole Tadeo,[1] Michael Okirwoth,[1] Darlisha A. Williams,[1,2] Edward Mpoza,[1] Lillian Tugume,[1] Kenneth Ssebambulidde,[1] Kathy Huppler Hullsiek,[2] Abdu K. Musubire,[1,4] Conrad Muzoora,[3] Joshua Rhein,[1,2] David B. Meya,[1,2,4] and David R. Boulware[2]

Adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis (ASTRO-CM)

Participants with high CSF lactate, >5.0 mmol/L, had significantly higher baseline

- CSF white cells (p=0.007)
- lower CSF glucose (p=0.0003)
- high CSF opening pressure
- (p=0.03)
- Glasgow coma score <15
- (p<0.0001)
- Baseline seizure (p=0.0006)



In multivariate analysis: After adjusting for **GCS, baseline seizures, OP, and quantitative CSF culture**,

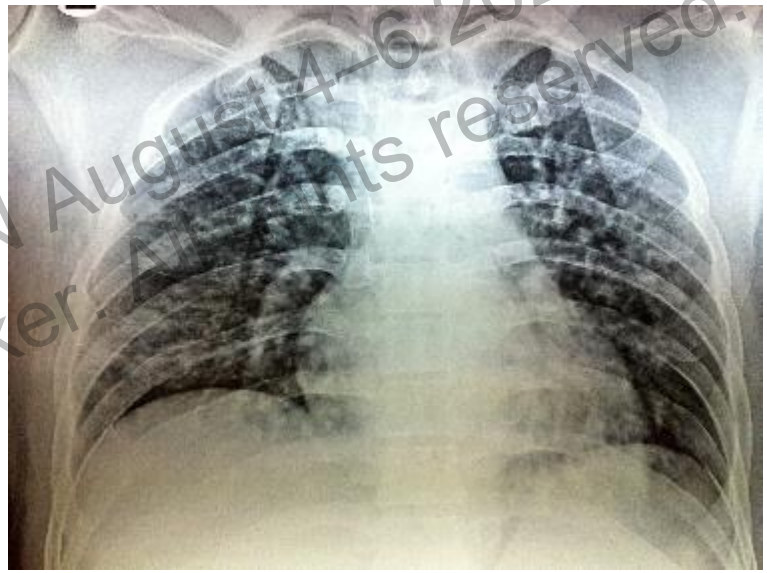
- High baseline CSF lactate continued to be at a 3-fold higher risk of mortality at 2 weeks compared with CSF lactate ≤3.0 mmol/L

[aHR], 3.41; 95% CI, 1.55–7.51; p=0.0021

Abassi M, et al. CID 2021;73(9):e3077-e308.

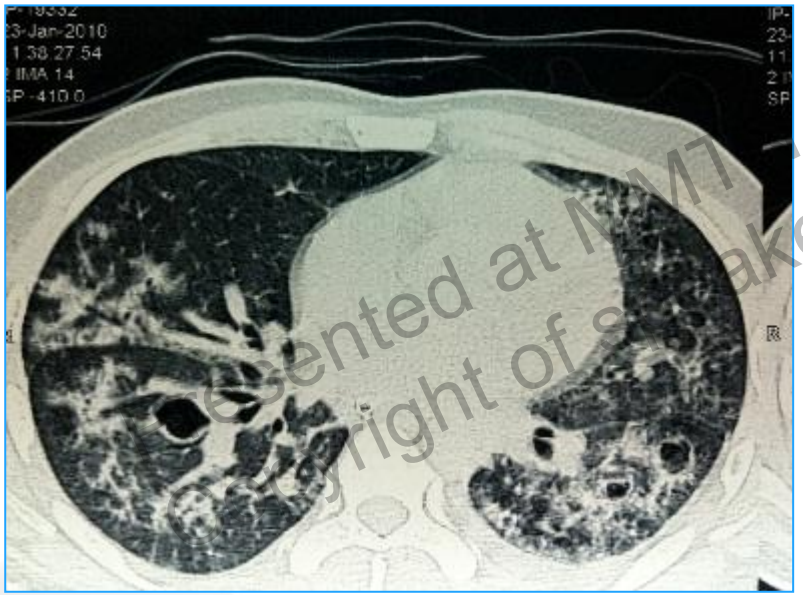
Patient remained well for 2 months after completion of treatment

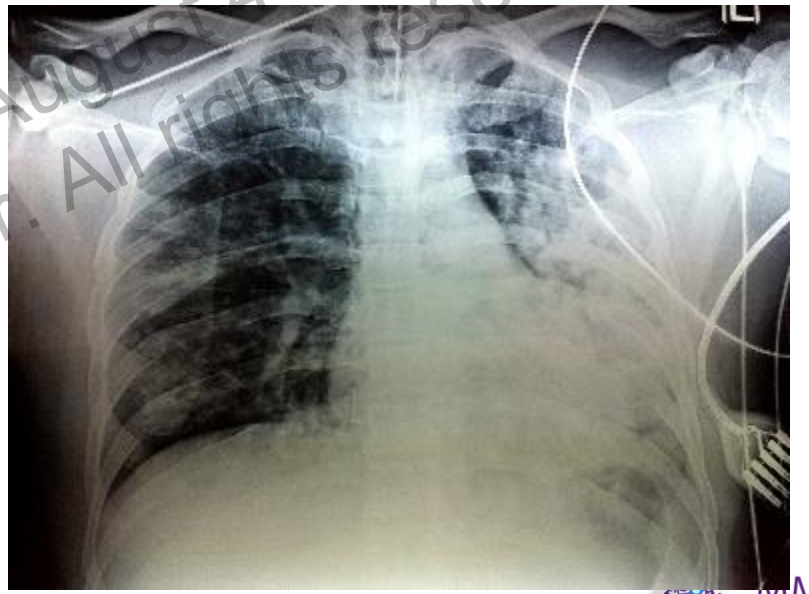
- Patient was admitted with severe headache, altered sensorium, fever, cough and breathlessness
- CSF examination:
  - Protein 156 mg/dL,
  - Sugar 30 mg/dL (120),
  - TC: 112/cmm (10% P, 90% L)
  - India Ink: Capsulated Yeasts +nt
- Treatment: Ceftriaxone, Amphotericin B deoxycholate 1 mg/kg
- Supportive care



Further course in hospital

- Progressive clinical deterioration over 1 week
- Breathless, intubation and mechanical ventilator





MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

Hospital course

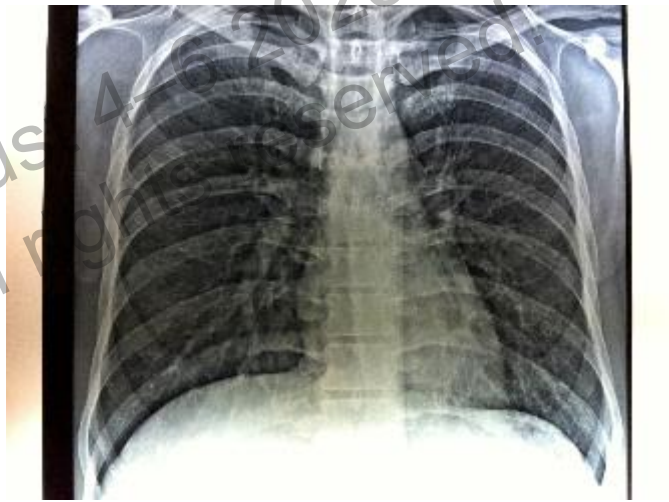
- Bronchoscopy: BAL showed plenty of capsulated yeasts suggestive of cryptococci
- **Infectious Diseases consult was taken**
- Reports available so far:
  - CSF: Cryptococcal culture positive for cryptococcus neoformans
  - Biochemistry was normal except hypokalemia

ID recommendations

- Further reports:
  - Cryptococcal antigen titer: 1:64
  - Repeat HIV testing: Non-reactive
  - CD4: 153 (8.87%)/cm3
  - Treatment changed to Amphotericin B deoxycholate (1 mg/kg/day) with 5-FC (100 mg/kg/day)

Case cont'd.

- Hospital course:
  - Tolerated treatment, renal injury (drug interruption) requires daily K Supplementation
  - Extubated after 8 days
  - Sensorium improved follows verbal commends
  - Requires repeated lumber drainage to control ICP
- Repeat CSF culture was positive after 2 weeks
  - D-AmB +5-FC continued for 8 weeks
  - CSF culture sent
- Consolidation: Fluconazole (800mg/day) + 5-FC **further two weeks**



Follow up CXR

How long do you intend to continue induction therapy in NHNT cryptococcal infections?

a) 2 weeks
b) 4–6 weeks
c) 8 weeks
d) Till patient achieves sterile CSF

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How long do you intend to continue induction therapy in NHNT cryptococcal infections?

ⓘ Start presenting to display the poll results on this slide.

N Engl J Med 1997;337:15-21

TREATMENT OF CRYPTOCOCCAL MENINGITIS ASSOCIATED WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME

CHARLES M. VAN DER HORST, M.D., MICHAEL S. SAAG, M.D., GRETCHEN A. CLOUD, M.S., RICHARD J. HAMILL, M.D., J. RICHARD GRAYBILL, M.D., JACK D. SOBEL, M.D., PHILIP C. JOHNSON, M.D., CARMELITA U. TUAZON, M.D., THOMAS KERKERING, M.D., BRUCE L. MOSKOVITZ, M.D., WILLIAM G. POWDERLY, M.D., WILLIAM E. DISMUKES, M.D., AND THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP AND AIDS CLINICAL TRIALS GROUP*

- Step 1: D-AmB + 5FC or D-AmB alone for two weeks
- Step 2: Fluconazole or Itraconazole
- **At two weeks**: CSF cultures were negative in 60% of the patients in combination arm and 51% of those who received D-AmB (P=0.06)
- **At ten weeks**: CSF cultures were negative in 72% (Flu) and 60% (ITR)
- **Mortality**: Step 1 : 5.5% (equal in both groups), Step 2: 3.9%

How should we treat Crypto in Non-HIV/Non-Transplant settings

- Heterogenous group: Apparently normal host, hematological malignancies to cirrhosis of liver
- No single therapeutic regimen
- **Induction**: L-AmB 3-4 mg/kg plus 5FC 100mg/kg/day for minimum two weeks
  - Consider extending induction therapy for C. gattii CNS infection to 4-6 weeks
  - Induction therapy may be extended in patients with persistently positive CSF cultures and/or persistent symptoms at two weeks
  - Alternative: ABLC 5mg/kg + 5FC, D-AmB 0.7-1.0 mg/kg +5FC, Flu 800-1200 mg/day +5FC

How should we treat Crypto in Non-HIV/Non-Transplant settings

- **Consolidation**: Fluconazole 400-800 mg/day 8 Weeks
  - Alternative: Voriconazole 200 BID, Posa 300 OD, Isavuconazole 200 OD, Itra 400 BID

- **Maintenance**: Fluconazole 200 mg 12 Months
  - Alternative Voriconazole, Posaconazole, Isavuconazole, Itraconazole

Case cont'd.

- CSF culture became sterile after 8 weeks
- Fluconazole 800 mg/day for 3 months
- After 3 months
- Fluconazole reduced to 400 mg/day
- He was continued with Fluconazole 200mg/day for rest of his life
- Repeat HIV: Non-reactive
- He remained in our follow up and developed PML after 7 years before he died

Timing	Baseline	9months	12 months
CD4 cells/mm^3	153 (8.87%)	210 (8%)	148 (9%)

Increased cryptococcal meningitis mortality among HIV negative, non-transplant patients: a single US center cohort study

Ther Adv Infectious Dis
2020, Vol. 7: 1–6
DOI: 10.1177/2049936120940881

Gabriel Motoa, Amy Pate, Daniel Chastain, Sarah Mann, Gregory S. Canfield, Carlos Franco-Paredes and Andrés F. Henao-Martínez

			Total ($n = 36$)	p value
		12)		
Age (years), mean (±SD, years)	42.2 ± 9.9	62.2 ± 7.4	48.8 ± 13.2	<0.001*
Sex, Male	21 (87.5)	9 (75)	30 (83.3)	0.343
White (%)	16 (66.7)	7 (58.3)	23 (63.9)	0.624
Clinical variables				
Median CSF WBC count/μL (IQR)	27.5 (12–63)	84 (53–265)	53 (14–118)	0.02*
Mean CSF glucose (±SD, mg/dl)	44 ± 17.2	25.6 ± 16.1	37.4 ± 18.8	0.005*
Median CSF protein (IQR, mg/dl)	57 (47–89)	171 (101–292)	89 (51–171)	0.001*
Opening pressure (cm H_2O)	30 (24–37)	29 (17–41)	30 (25–35)	0.8
Altered mental status (%)	6 (25)	7 (58.3)	13 (36.1)	0.05
ICU admission (%)	5 (20.8)	5 (41.7)	10 (27.8)	0.188
Mortality rate				
90-days (%)	2 (8.3)	5 (41.7)	7 (19.4)	0.017
1-year (%)	3 (12.5)	5 (41.7)	8 (22.2)	0.047

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2016, 0, 1–8
doi: 10.1093/mmy/myw021
Advance Access Publication Date: 0 2016
Original Article

Original Article

Cryptococcosis in non-HIV/non-transplant patients: A Brazilian case series

Naiane Ribeiro Lomes[1], Marcia Souza de Carvalho Melhem[2],

- 20% Mortality
- Aggressive ICP management
- AMB combination with Flu or 5FC in 93.1%

Review of 53 Cases of Cryptococcosis and Idiopathic CD4 cytopenia

Parameter	Results (n = 53)
Age median/ Male	41 years/ 55%
Site of cryptococcosis CNS Pulmonary Bone disease	 75% 11% 8%
CSF findings WBC median Glucose Protein	 59/mm^3 36 mg/dL 156 mg/dL
CD4+ cell at diagnosis (median)	82/mm^3
Outcome Improved Cure Relapsed Mortality Not Specified	 28 (52.8%) 8 (15%) 6 (11.3%) 4(7.5%) 7 (13.2%)

Treatment	n (%)
Amphotericin B	18 (33.9)
Amphotericin B + flucytosine	12 (22.6)
Fluconazole	10 (18.8)
NS	9 (16.9)
Amphotericin B + fluconazole	2 (3.7)
Amphotericin B + itraconazole	1 (1.8)
Amphotericin B + flucytosine + IFN-g	1 (1.8)

Zonios DI, Medicine (Baltimore). 2007 Mar;86(2):78-92.

Take Home Message

- Cryptococcosis in NHNT host is difficult to treat
- Requires prolonged Induction therapy
- Higher inflammations into the CSF
- May require prolonged secondary prophylaxis to prevent recurrence

Thank you