
City of Hope

RARE INFECTION IN HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

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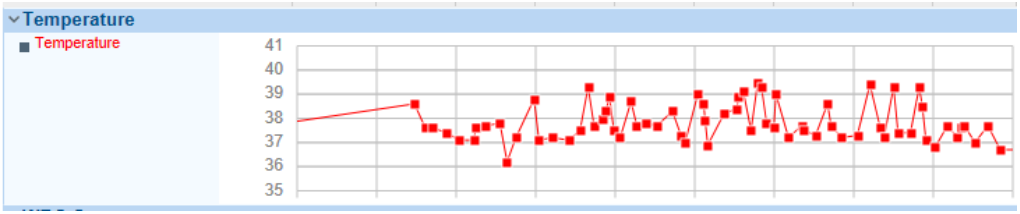
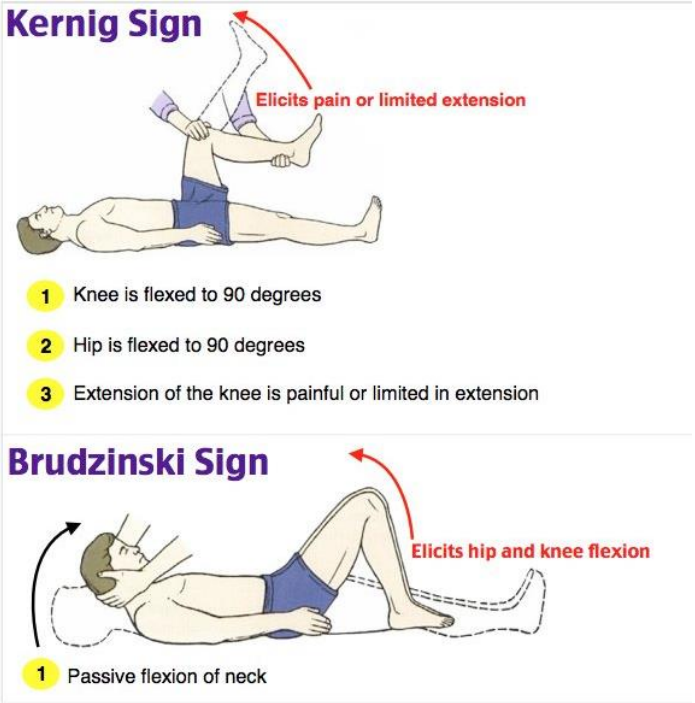
Case presentation

- HPI: Mrs. RS is a 58 y.o. Caucasian female with history of Hodgkin lymphoma diagnosed in 1991, was hesitant to undergo chemotherapy and received radiation to left neck and axilla, relapsed in 1997 and was treated with 6 cycles of ABVD, then developed DLBCL in 2018 and achieved CR1 with RCEP in late 2018 but relapsed in 11/2022 (with disease above and below diaphragm), received 2 cycles of R-CHOP and 1 cycle or R-CVP leading to CR2, followed by autologous HSCT with BEAM conditioning on 4/20/23, currently in remission, with post-transplant course c/b SARS-CoV-2 infection with prolonged shedding from 4/2023-6/2023, who presented in 7/2023 with a 4-day history of fever, chills, headaches and neck stiffness.
- PMH: Per HPI
- PSH: Tonsillectomy
- Fam Hx: Non-contributory
- Allergies: Ciprofloxacin – bone pain
- Medications: Acyclovir, bactrim
- Soc Hx: Lives in Riverside with her husband. Used to work in her church office and with many children but not since the past 5+ years. Denies tobacco, recreational drug, or EtOH use. Has a pet dog and cat and is exposed to her daughter's and son's dogs. Prior PPDs have been negative, none recent. Loves to garden. No mold issues at home. No recent construction/renovations at home. Likes to swim and use the sauna but not since summer 2022. No international travel within the past 5 years. Usually travels locally within California.

Case presentation (cont.)



GENERAL: Awake, alert, **uncomfortable due to headache**, laying flat on the bed, appears anxious
HEENT: PERRLA, EOMI, photophobia, sclera anicteric, no oral ulcers, no sinus tenderness to palpation, dentition fair
NECK: **Nuchal rigidity**
CARDIOVASCULAR: RRR, normal s1 s2, no m/r/g
PULMONARY: CTA bilaterally, unlabored breathing, on room air
ABDOMEN: Soft, non-tender, non-distended, normoactive bowel sounds
EXTREMITIES: No c/e/e
SKIN: No rashes
NEURO: **AOx4, CN II-XII intact, no gross deficits**
LDAs: Right port-a-cath 3/13/23



Labs

GENERAL HEMATOL...					
WBC Count	6.26	6.34	4.97	5.16	3.64 ↓
RBC Count	2.57 ↓	2.40 ↓	2.28 ↓	2.25 ↓	2.11 ↓
Hemoglobin	8.6 ↓	8.3 ↓	7.8 ↓	7.8 ↓	7.3 ↓
Hematocrit	26.3 ↓	25.0 ↓	23.7 ↓	23.3 ↓	21.6 ↓
Platelet Count	78 ↓	79 ↓	69 ↓	66 ↓	49 ↓
MCV	102.3 ↑	104.2 ↑	103.9 ↑	103.6 ↑	102.4 ↑
MCH	33.5 ↑	34.6 ↑	34.2 ↑	34.7 ↑	34.6 ↑
MCHC	32.7	33.2	32.9	33.5	33.8
RDW	14.3	14.4	14.6	14.1	14.2
MPV	11.4	11.7	11.7	11.6	11.6
Segmented Neutrophil Percent	77.7 ↑	71.4	80.9 ↑	69.7	83.4 ↑
Neutrophils %					
Lymphocyte Percent	11.2 ↓	12.2 ↓	10.0 ↓	16.9 ↓	12.5 ↓
Lymphocytes%					
Monocyte Percent	3.4 ↓	8.7	5.0	2.5 ↓	1.7 ↓
Monocytes%					
Eosinophil Percent	0.0 ↓	0.0 ↓	0.8	2.5	0.8
Eosinophils%					
Basophil Percent	0.0 ↓	1.7 ↑	0.0 ↓	0.0 ↓	0.0 ↓
Basophil %					
Segmented Neutrophil Absolute	4.86	4.53	4.02	3.60	3.04
Absolute Neutrophils					
Lymphocyte Absolute	0.70 ↓	0.77 ↓	0.50 ↓	0.87 ↓	0.46 ↓
Absolute Lymphoctyes					
Monocyte Absolute	0.21 ↓	0.55	0.25 ↓	0.13 ↓	0.06 ↓
Absolute Monocytes					
Eosinophil Absolute	0.00 ↓	0.00 ↓	0.04	0.13	0.03
Absolute Eosinophils					
Basophil Absolute	0.00 ↓	0.11 ↑	0.00 ↓	0.00 ↓	0.00 ↓
Absolute Basophils					
NRBC %	0.0	0.0	0.0	0.0	0.0
Absolute NRBC	0.00	0.00	0.00	0.00	0.00

GENERAL CHEMISTRY	
Protein Total, Blood	6.3
Albumin Level, Blood	3.8
Calcium Level, Blood	8.9
Bilirubin Total, Blood	0.3
Bilirubin Conjugated (Direct), Blood	
Alkaline Phosphatase Level, Blood	114
ALT (SGPT)	15
AST	24
Sodium Level, Blood	135 ↓
Potassium Level, Blood	3.7
Chloride Level, Blood	103
Carbon Dioxide Level, Blood	24
Glucose Level (Random), Blood	105
Blood Urea Nitrogen Level, Blood	11
Creatinine Level, Blood	0.85
eGFR African American	>=60
eGFR Except African American	>=60
Anion Gap, Blood	8
Magnesium Level, Blood	
Phosphorus Level, Blood	
Albumin / Globulin Ratio	1.5

CD4 count

	Ref Range & Units
Percent T-cell (CD3+) Count	83.39
56.00 - 86.00 %	
Absolute T-cell (CD3+) Count	618 ↓
723 - 2,737 cells/uL	
Percent T Suppressor Cell (CD3+CD8+) Count	62.07 ↑
13.00 - 39.00 %	
Absolute T Suppressor Cell (CD3+CD8+) Count	462
220 - 1,129 cells/uL	
Percent T Helper Cell (CD3+CD4+) Count	22.04 ↓
33.00 - 58.00 %	
Absolute T Helper Cell (CD3+CD4+) Count	164 ↓
401 - 1,612 cells/uL	
Helper/Suppressor Ratio	0.4 ↓
0.7 - 3.6	
Percent NK cell (CD16+CD56+CD3-) Count	15.90
5.00 - 26.00 %	
Absolute NK cell (CD16+CD56+CD3-) Count	117
84 - 724 cells/uL	
Percent B-cell (CD19+) Count	0.00 ↓
5.00 - 22.00 %	
Absolute B-cell (CD19+) Count	<25 ↓
80 - 616 cells/uL	

Other labs available before CSF analysis

- Blood cultures: Negative
- Serum Cryptococcal antigen: Negative

CSF analysis

IMPRESSION:

1. Fluoroscopic guided lumbar puncture, with no immediate complications.
2. Opening pressure = 10 cm.

CSF TESTING		
WBC Count, Cerebrospinal Fluid		9 ▲
RBC Count, Cerebrospinal Fluid		27
Protein, CSF		134 ▲
Glucose Level, CSF		42

Total Counted, Cerebrospinal Fluid	100
Segmented Neutrophil Percent, Cerebrospinal Fluid %	39.0
Lymphocyte Percent, Cerebrospinal Fluid %	50.0
Monocyte Percent, Cerebrospinal Fluid %	10.0
Basophil Percent, Cerebrospinal Fluid %	1.0

Serum total protein 6.6 g/dL
Serum glucose 100 mg/dL

Differential diagnosis?

And the CSF analysis ultimately yielded…

A. Bartonella henselae (PCR+)
B. Capnocytophaga canimorsus
C. Coccidioides immitis
D. Cryptococcus neoformans
E. HSV (PCR+ from multiplex panel)
F. Mycobacterium kansasii

CSF analysis

Cryptococcal Ag Screen, CSF Negative	**Positive !**
Cryptococcal Ag Titer, CSF <1:1	**1:160 ^**
Fungus Culture	Rare Cryptococcus neoformans !
Fungus Stain	No fungal elements seen

Meningitis/Encephalitis Panel, PCR

Status: **Final result** Visible to patient: **No (not released)**
Next appt: **07/28/2023 at 02:20 PM in Lab (MM VAD CHAIR 02)**
Specimen Information: CSF (Specify); Cerebrospinal Fluid (CSF)

0 Result Notes

Component	
Escherichia coli K1 by PCR	Not Detected
Haemophilus influenzae by PCR (ARUP)	Not Detected
Listeria monocytogenes by PCR (ARUP)	Not Detected
Neisseria meningitidis by PCR (ARUP)	Not Detected
Streptococcus agalactiae by PCR (ARUP)	Not Detected
Streptococcus pneumoniae by PCR (ARUP)	Not Detected
Cytomegalovirus by PCR (ARUP)	Not Detected
Enterovirus by PCR (ARUP)	Not Detected
Herpes simplex virus 1 by PCR (ARUP)	Not Detected
Herpes simplex virus 2 by PCR (ARUP)	Not Detected
Human herpesvirus 6 by PCR (ARUP)	Not Detected
Human parechovirus by PCR (ARUP)	Not Detected
Varicella zoster virus by PCR (ARUP)	Not Detected
Cryptococcus neoformans/gattii by PCR (ARUP)	**Detected !**

False-negative serum CrAg screen

Cryptococcal Antigen Screen, Blood Negative	Negative	
Cryptococcal Ag Titer, Blood <1:1		1:80 ^

Several reasons have been proposed:

- A low level of cryptococcal antigen
- Presence of non-specific proteins that may mask the cryptococcal antigen
- **Post-zone phenomenon**
  - First described by Stamm and colleagues in 1980
  - False-negative test caused by excessive antigen relative to antibodies
    - Very high concentrations of Cryptococcal antigen in a sample out-compete the antigen-antibody complex in the test strip for binding on the anti-CrAg monoclonal antibodies in the test line
    - In the absence of significant binding with the labeled antigen-antibody complex, the test line remains difficult to visualize and is typically read as negative

Additional data?

Would you send out the isolate for antifungal susceptibility testing?

A. Yes

B. No

CSF analysis

Fungus Culture	Rare Cryptococcus neoformans !
	Susceptibility to Follow
Fungus Stain	No fungal elements seen

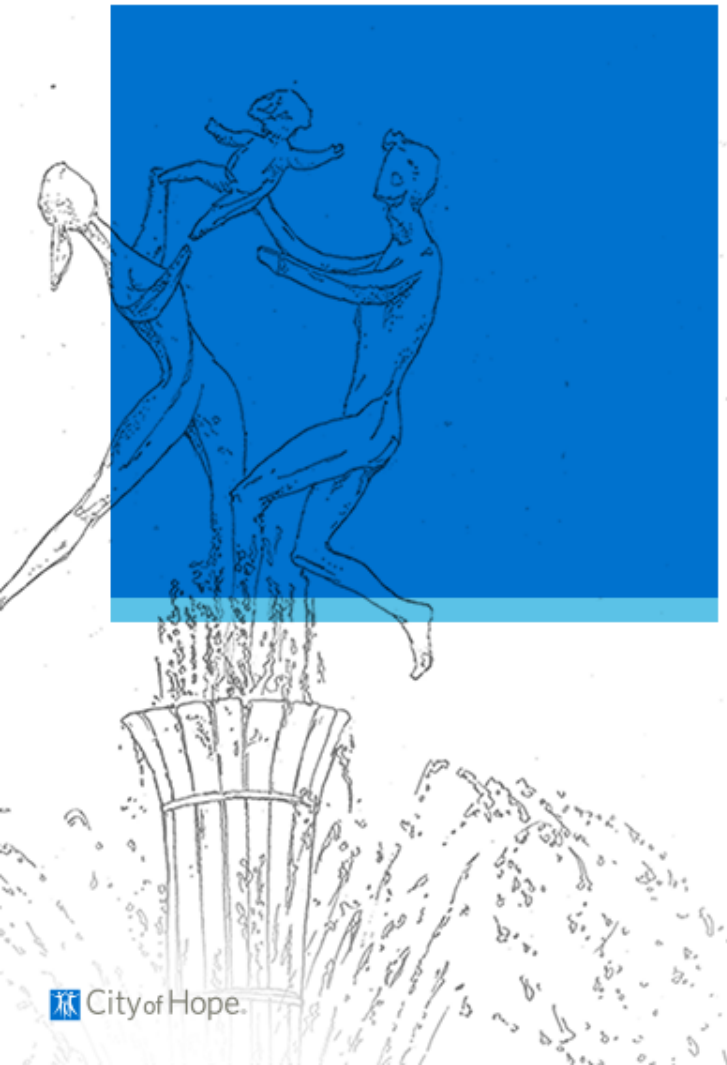
Comment: Cryptococcus neoformans
Organism identified by client
YSTMIC
Fluconazole 8
Not all antifungal drugs attain adequate concentrations in all body sites. See the ARUP LTD for additional information. If testing and reporting additional antifungal agents is required, please contact the laboratory.
Voriconazole 0.12
Not all antifungal drugs attain adequate concentrations in all body sites. See the ARUP LTD for additional information. If testing and reporting additional antifungal agents is required, please contact the laboratory.
Amphotericin B 1
Not all antifungal drugs attain adequate concentrations in all body sites. See the ARUP LTD for additional information. If testing and reporting additional antifungal agents is required, please contact the laboratory.
Interpretive Information See Note
At the present time there are no CLSI guidelines for performance and/or interpretation of susceptibility testing for the above organism and/or the indicated antimicrobial agent(s).
Performed By: ARUP Laboratories

Imaging

CT chest w/o contrast: 1. No acute abnormality. 2. Small hypoenhancing inferior splenic lesion likely representing lymphoma, decreased in size from 10/25/2022. 3. Mosaic attenuation pattern throughout the lungs suggestive of gas trapping. 4. Stable areas of bandlike atelectasis versus scarring within the bilateral upper lobes. 5. Stable nonspecific 7 mm right middle lobe nodule and a few other scattered pulmonary micronodules.

MRI brain w/wo contrast: 1. No evidence of intraparenchymal mass lesion or acute territorial infarction. 2. Questionable areas of FLAIR abnormality within a few sulci which could represent meningitis changes but are nonspecific.

Outline



- Background
- Management
- Antifungal resistance mechanisms
- Emerging treatment modalities

Background

- More than 30 species of the genus *Cryptococcus* have been described, but infection in humans primarily caused by *C. neoformans* and *C. gattii*
- Uncommon infection among HSCT recipients
  - TRANSNET Database from 2001-2006: 6 cases among 875 HSCT recipients and 12-month cumulative incidence 0.4%
  - Decreased incidence in this population, in contrast to SOT recipients, may be related to the widespread use of azole antifungal prophylaxis or differences in immunosuppression
- Timing of infection has ranged from pre-transplant to 6 months post-transplant
- Thymic regeneration in HSCT recipients may render T cells more effective against *Cryptococcus* species
- T-helper 1 (Th1) cell response characterized by the production of proinflammatory cytokines (e.g., interferon-gamma) is protective against cryptococcosis
  - In HSCT recipients, the conditioning regimen results in damage to the host tissue, especially the intestinal mucosa, and stimulates the secretion of inflammatory cytokines
  - In allogeneic HSCT recipients, these cytokines further activate antigen-presenting cells and, ultimately, donor T cells, leading to the proliferation of Th1 cells
- T-helper 2 (Th2) cell response with the induction of interleukin 10 is associated with disease progression
  - In autologous HSCT recipients, the production and messenger RNA expression of Th1 cytokines is severely impaired, whereas the levels of Th2 cytokines is relatively high
  - This may account for the susceptibility of autologous HSCT recipients to cryptococcal disease

Management

Table 3. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Transplant Recipients

Regimen	Duration	Evidence
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)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day)[b]	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

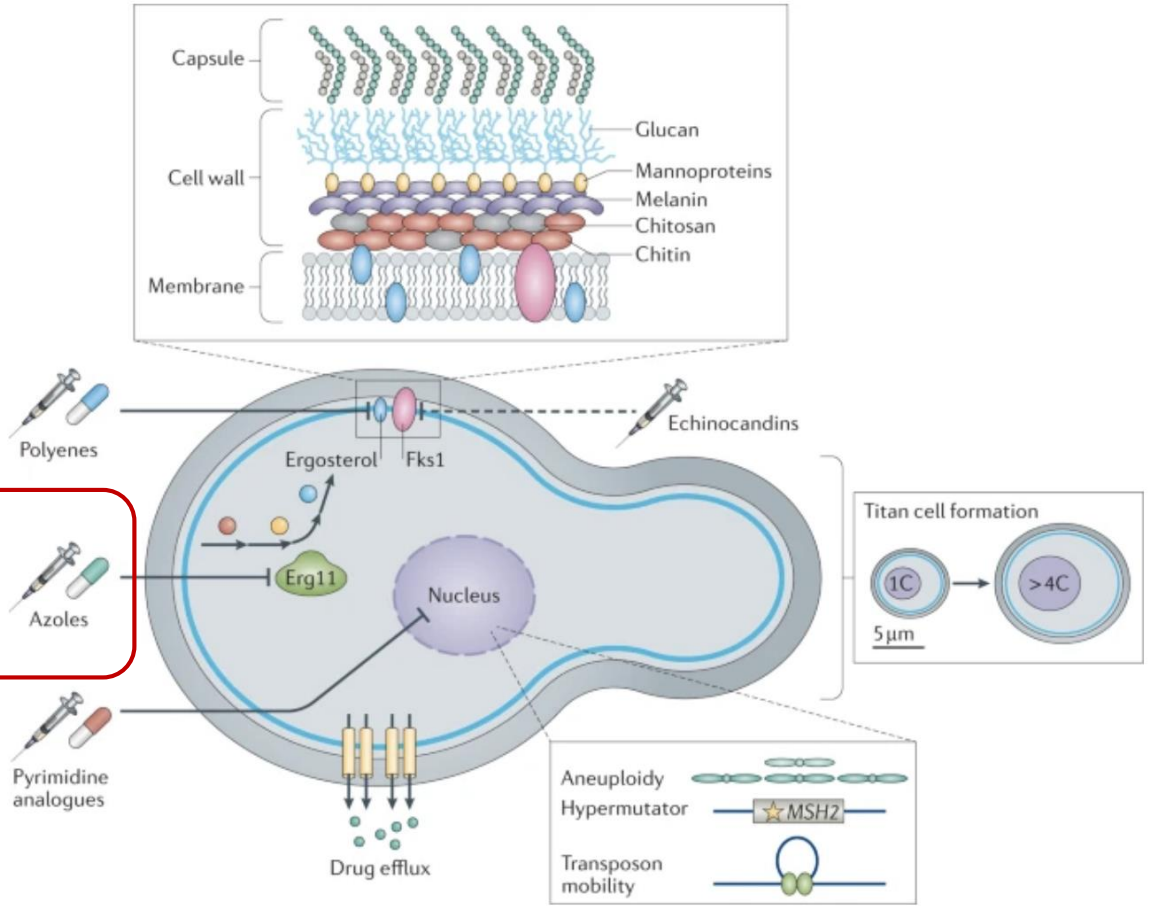
[a] Immunosuppressive management may require sequential or step-wise reductions.

[b] Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction with calcineurin inhibitors are important and the effective dose is imprecise.

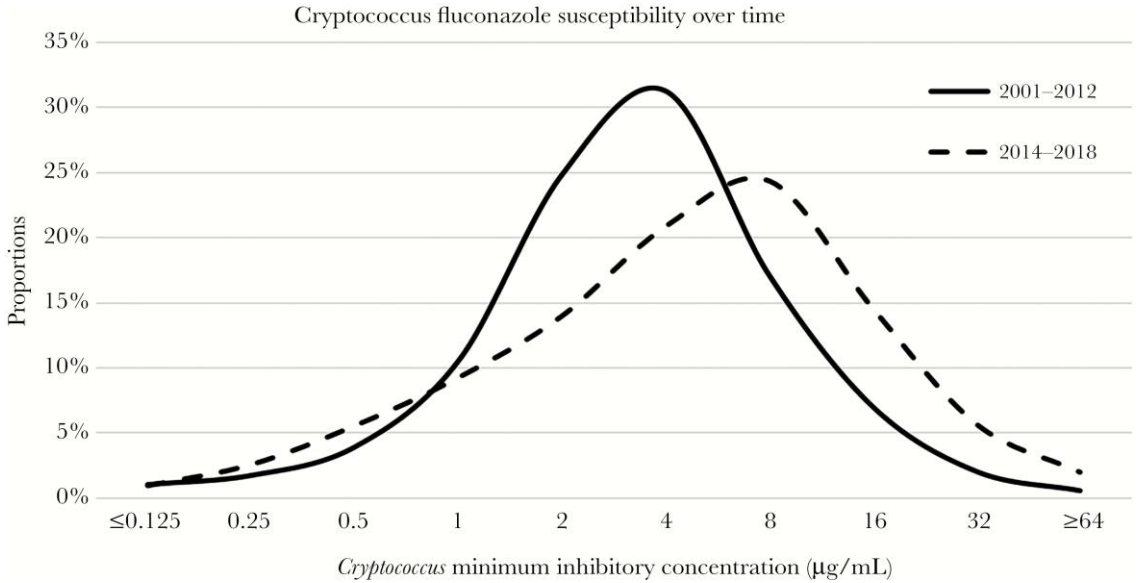
Resistance mechanisms to current agents

- Overexpression or alteration of the drug target
- Inactivation of proteins required for drug target engagement
- Increased expression of efflux pumps

Fig. 1: Mechanisms governing resistance to current antifungal agents in *Cryptococcus* spp.



Fluconazole MIC distribution for Cryptococcus



- Prevalence of fluconazole non-susceptible *Cryptococcus* is increasing over time, risking the efficacy of long-established standard dosing
- Chesdachai and colleagues summarized 21 studies with 11,049 clinical *Cryptococcus* isolates
  - The median MIC_{50} trended upwards from 4 µg/mL in 2000-2012 to 8 µg/mL in 2014-2018

Single, high dose liposomal amphotericin B

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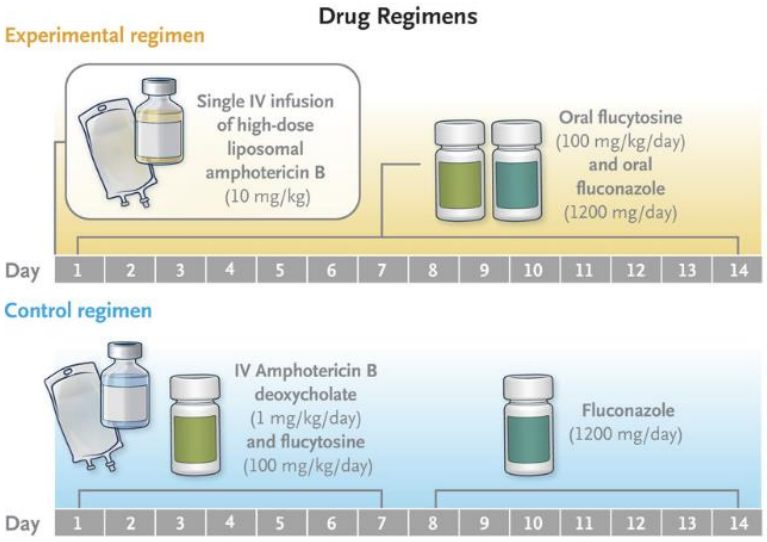
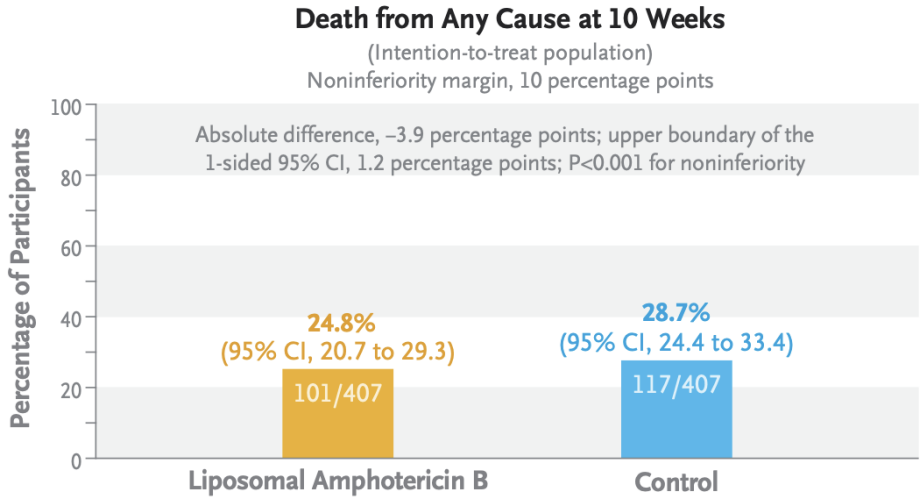
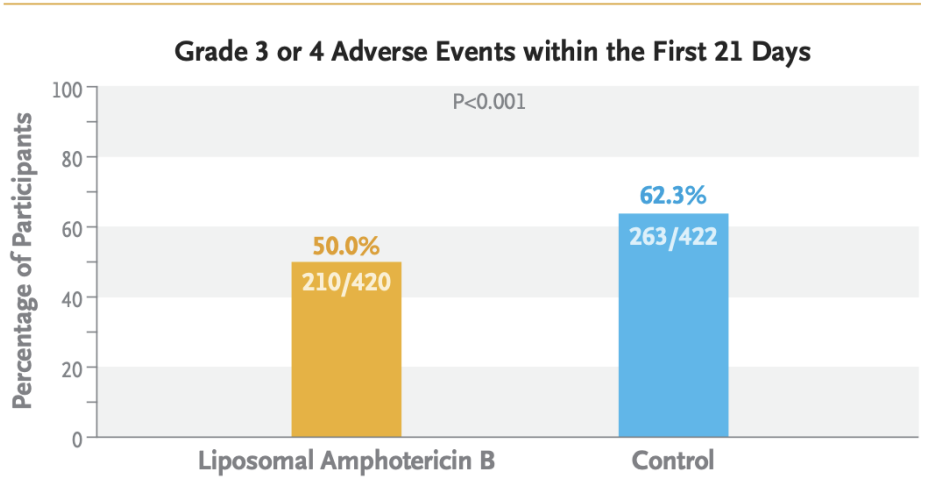
Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

J.N. Jarvis, D.S. Lawrence, D.B. Meya, E. Kagimu, J. Kasibante, E. Mpoza, M.K. Rutakingirwa, K. Ssebambulidde, L. Tugume, J. Rhein, D.R. Boulware, H.C. Mwandumba, M. Moyo, H. Mzinganjira, C. Kanyama, M.C. Hosseinipour, C. Chawinga, G. Meintjes, C. Schutz, K. Comins, A. Singh, C. Muzoora, S. Jjunju, E. Nuwagira, M. Mosepele, T. Leeme, K. Siamisang, C.E. Ndhlovu, A. Hlupeni, C. Mutata, E. van Widenfelt, T. Chen, D. Wang, W. Hope, T. Boyer-Chammard, A. Loyse, S.F. Molloy, N. Youssouf, O. Lortholary, D.G. Lalloo, S. Jaffar, and T.S. Harrison, for the Ambition Study Group*

Single, high dose liposomal amphotericin B







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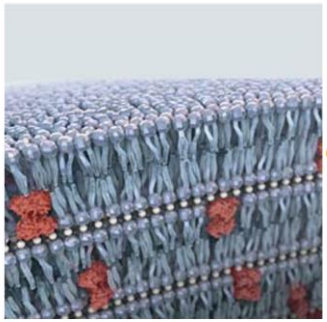
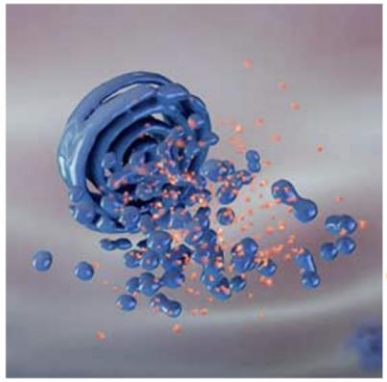
MAT2203 (oral lipid nanocrystal amphotericin B)



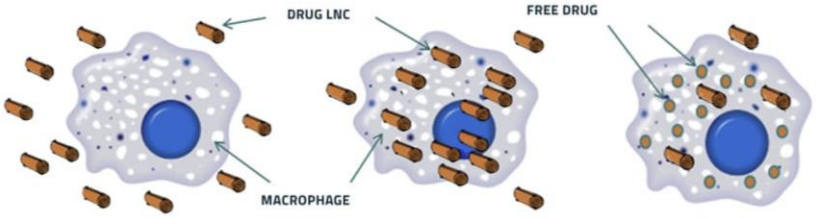
DRUG ENCAPSULATION

1. The cochleate is prepared using naturally occurring phospholipids and calcium.
2. When calcium interacts with the negatively charged lipids, they spiral into non-toxic, highly stable crystalline units with multiple layers and little to no internal aqueous space.
3. The active drug molecules become trapped within the layers, where they are protected from water and harmful external elements.



INTRACELLULAR RELEASE

4. The cochleate is delivered into the body and directly targets the clinically relevant cells.
5. It then fuses with the cell membrane in a non-destructive manner.
6. The low calcium environment of the cell's interior causes the cochleate to unlock and unwind, releasing the drug into the target cell.



LNC MODEL

- Lower plasma levels of active drug
- Enters cells directly, releasing the drug content into the infected cell membrane
- Likely to result in less systemic toxicity

MAT2203 (oral lipid nanocrystal amphotericin B)

MAT2203 (oral lipid nanocrystal amphotericin B)

Encochleated Oral Amphotericin for Cryptococcal Meningitis Trial (EnACT)

PHASE 2

OBJECTIVE

An NIH-funded, prospective randomized trial evaluating the safety, tolerability and efficacy of MAT2203 in HIV-infected patients with cryptococcal meningitis, compared to treatment with standard IV-administered amphotericin B as induction therapy. It will ultimately assess the potential for all-oral induction and maintenance therapy with MAT2203.

OVERVIEW

Study Population: 140 patients

Inclusion Criteria: HIV-infected patients with cryptococcal meningitis.

Trial Design: 100 patients will receive MAT2203 and flucytosine (5-FC) in 4 stages, with escalating durations of MAT2203 and decreasing durations of IV amphotericin B. In cohorts 2 and 4, 40 control patients will receive the standard of care – IV-administered amphotericin B and 5-FC. Patients will receive induction treatment for 14 days, followed by consolidation therapy for up to 10 weeks. An independent Data Monitoring Committee assured safety and efficacy throughout the trial.

Results: Analyses of final data from Cohort 2 of EnACT demonstrated (i) survival at Day 30 (early survival) of 98% in patients receiving MAT2203 vs. 88% in patients receiving IV Amphotericin B (SOC); and (ii) culture conversion (sterility) assessed at any time during the trial of 97% in patients receiving MAT2203 and 76% in patients receiving SOC.

Interim results from Cohort 4, which evaluated the safety and efficacy of an all-oral regimen of MAT2203, were presented at IDWeek 2022. CSF yeast clearance rate exceeded the prespecified primary endpoint threshold target of >0.20, interim survival is currently 90%, while the survival rate at Week 2 was 95%; note that Week 2 survival is the prespecified primary endpoint for the MAT2203 Phase 3 registration trial in cryptococcal meningitis.

MAT2203 (oral lipid nanocrystal amphotericin B)

Study Overview

Brief Summary:
This pivotal, confirmatory trial seeks to independently verify the results observed in the EnACT Phase II Stage 2 trial (MB-70007).

Detailed Description:
Pivotal, prospective, randomized, open-label, non-inferiority trial to compare the efficacy and safety of step-down induction and consolidation therapy for the treatment of cryptococcal meningitis with oral MAT2203 plus flucytosine to standard of care therapy. Randomization will by 1:1:1 to one of two experimental arms or standard of care.

OFFICIAL TITLE

Encochleated Oral Amphotericin for Cryptococcal Meningitis Trial 3

CONDITIONS

Cryptococcal Meningitis

INTERVENTION / TREATMENT

Drug: MAT2203

Drug: Amphotericin B

STUDY START (ESTIMATED)

2023-01

PRIMARY COMPLETION (ESTIMATED)

2024-10

STUDY COMPLETION (ESTIMATED)

2025-01

ENROLLMENT (ESTIMATED)

270

STUDY TYPE

Interventional

PHASE

Phase 3

OTHER STUDY ID NUMBERS

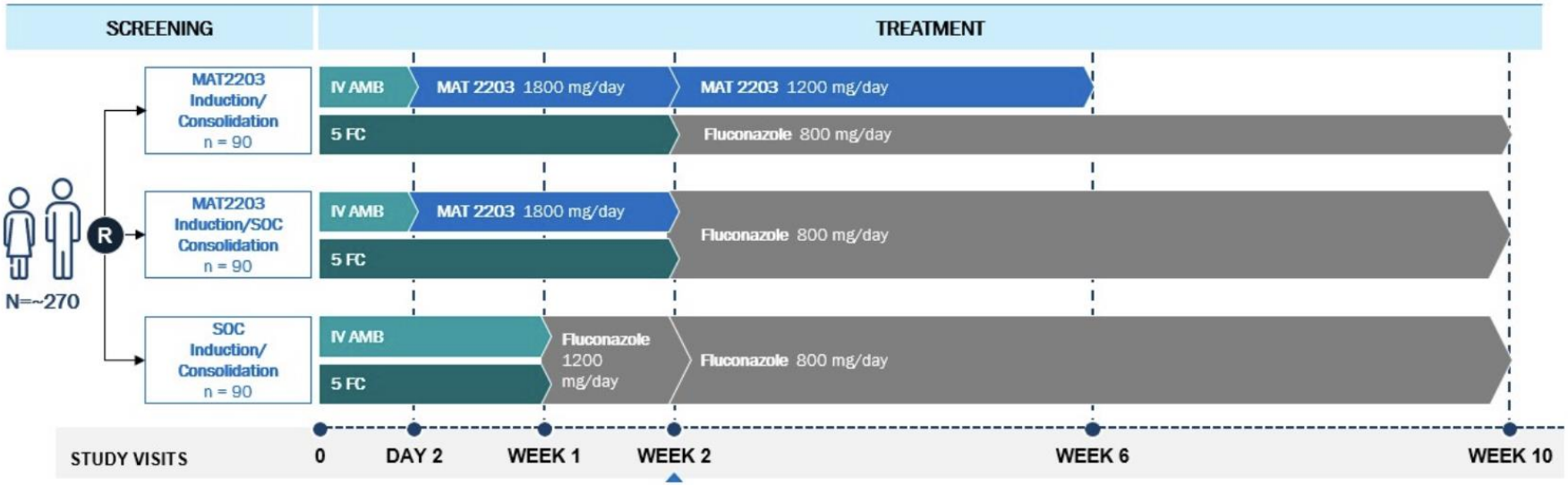
MB-70018

CTA 0217 (Other Identifier) (OTHER: Uganda National Drug Authority (NDA))

Resource links provided by the National Library of Medicine
NIH NLM +

MAT2203 (oral lipid nanocrystal amphotericin B)

Phase III Pivotal Study Design to Assess MAT2203 as step-down therapy after 2 days of IV AMB for the Treatment of Cryptococcal Meningitis

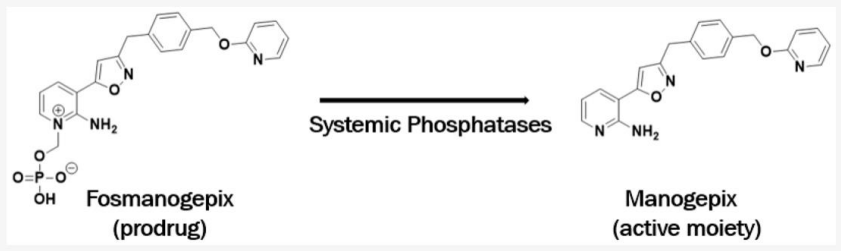


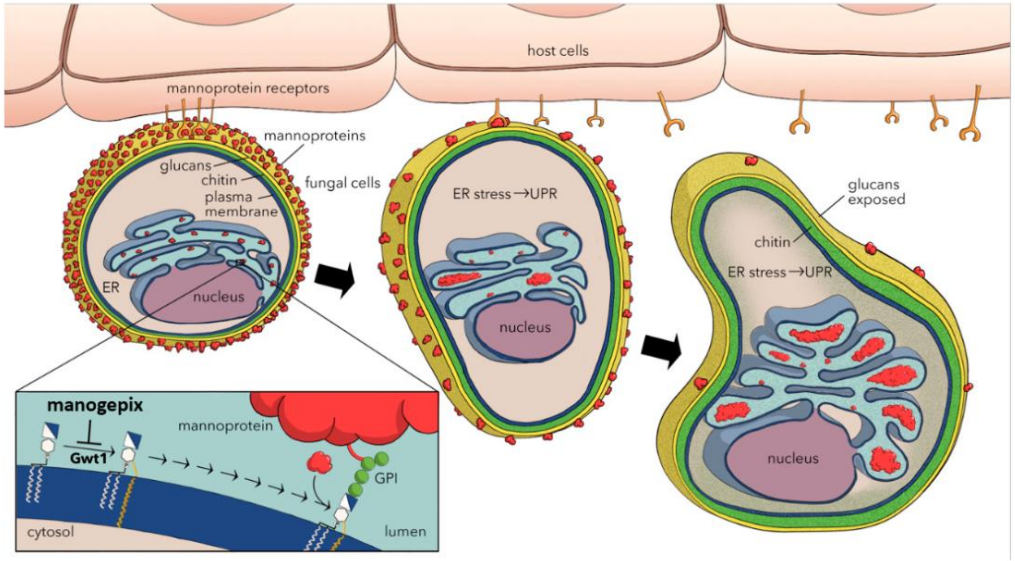
- Study Initiation Q1 2023
- NDA Filing H1 2025

PRIMARY ENDPOINT:
All-cause mortality at 2 weeks in non-inferiority trial; NI Margin 10%

Key Secondary Efficacy Endpoint:
Survival time through 10 weeks without *Cryptococcus* culture-positive relapse of meningitis

APX001 (fosmanogepix)





- Inhibits Gwt1, a target specific to fungal cells
- Gwt1 inhibition blocks mannoprotein transport
- Lack of mannoproteins on cell wall and stress response lead to fungal cell death
- Broad spectrum
- Wide tissue distribution
- Favorable safety and DDI profile
- Fast track status and orphan drug designation by the US FDA for 7 infections including cryptococcosis

My patients

- Current patient
  - Induction therapy: Ambisome 3mg/kg/day + flucytosine 100mg/kg/day
  - Repeat LP (*done in 28 days due to obstacles with insurance coverage*): WBC 32, lymph 89%, mono 8%, macro 3%, RBC 0, protein 73, glucose 53; CSF CrAg 1:5, CSF fungal stain/culture negative
  - Repeat serum CrAg 1:10
  - Currently on consolidation therapy with voriconazole
- Another patient
  - [redacted] with history of idiopathic CD4/CD8 lymphopenia complicated by disseminated cryptococcal infection in [redacted]7/2019, maintained on posaconazole, was then diagnosed with peripheral T-cell lymphoma in [redacted]3/2022, achieved CR with BV-CHP and subsequently underwent MUD allogeneic HSCT with fludarabine/melphalan conditioning (cyclophosphamide/tacrolimus/MMF GvHD prophylaxis) on 6/29/23, who developed Cryptococcal meningitis on 7/26/23, with course c/b ambisome-induced renal insufficiency.
  - Currently on MAT2203 under a single patient emergency IND

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Thank you!

Questions? Comments?


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