Early fungicidal activity as surrogate endpoint for cryptococcal meningitis survival

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BACKGROUND

- Globally, cryptococcal meningitis causes 15% of AIDS-related deaths.
- Antifungal therapies exist, but less toxic, more effective therapies are needed. One hindrance to investigating new therapies is the length of time trials take when using all-cause mortality (ACM) as a primary endpoint.
- Early fungicidal activity (EFA) has been used as a surrogate for ACM. Several studies have reported a relationship between EFA and ACM through 10-weeks.
- We sought to investigate the association between EFA and ACM through 18-weeks using a large cohort of cryptococcal meningitis participants enrolled in sequential clinical trials.

METHODS

- Individual-level CSF data from three sequential cryptococcal meningitis clinical trials conducted during 2010- 2017 were pooled (COAT, n=162; ASTRO-CM pilot, n=179; ASTRO-CM RCT, n=397)
- During COAT, CSF quantitative cultures (QCC) were performed on days 1, 7, 14, and additionally as needed for intracranial pressure (ICP) control. During ASTRO-CM trials, QCCs were performed on days 1, 3, 7, 10-14, and as needed for ICP control.
- To minimize survival bias, we limited contributions of cultures to the first 10 days of antifungal therapy.
- Once calculated, EFA measurements were divided into four groups: 0.40 $\log_{10}$CFU/ml/day, 0.30 to 0.39 $\log_{10}$CFU/ml/day, 0.20 to 0.29 $\log_{10}$CFU/ml/day, and less than 0.20 $\log_{10}$CFU/ml/day.
- Cumulative survival of each group was plotted against time in a Kaplan-Meier curve **(Figure 1),** with a total follow-up time of 18-weeks.
- Survival time was compared with a log-rank test, and risk factor adjustments were made via Cox regression.

CSF Yeast Clearance Rate <0.20 $\log_{10}$ CFU/mL/day was associated with increased 18-week mortality in cryptococcal meningitis. This EFA threshold may be a surrogate marker for Phase II Trials

RESULTS

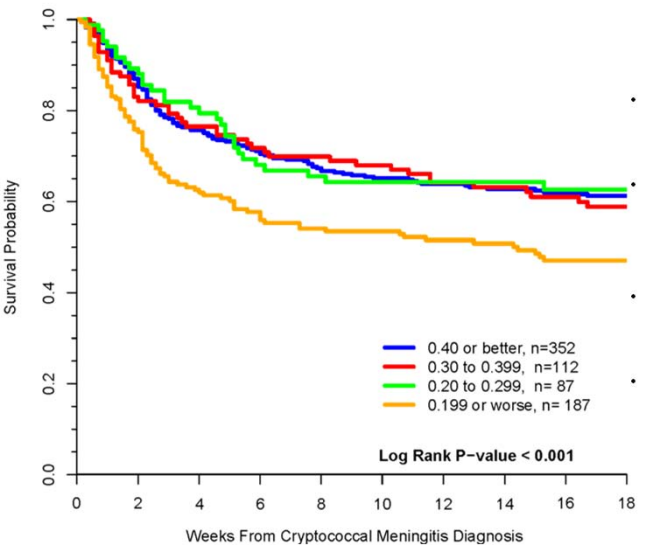
- Analysis includes 738 subjects with a calculable EFA within the first 10 days of meningitis diagnosis.
- Full demographic break down by EFA grouping is given in **Table 1**.
- 18-week mortality rates were 37%, 39%, 36%, and 50% for the EFA group, from highest (≥0.40) to lowest (<0.20), respectively.

Table 1. Characteristics and outcomes by EFA group

	EFA Group, $\log_{10}$ CFU/mL/day				
	0.40 or greater	0.30-0.39	0.20-0.29	0.19 or less	P-value
N	352	112	87	187	
Age, years	35 [29, 41]	36 [30, 41]	35 [30, 38]	35 [30, 40]	.73
Men	203 (58%)	71 (63%)	50 (58%)	127 (68%)	.11
Prior Cryptococcosis	30 (9%)	6 (5%)	12 (14%)	22 (12%)	.13
Receiving ART	131 (37%)	35 (31%)	41 (47%)	70 (37%)	.15
TB Diagnosis at baseline	20 (5.7%)	8 (7.1%)	8 (9.2%)	16 (8.6%)	.52
Glasgow Coma Scale < 15	140 (40%)	43 (38%)	36 (41%)	68 (37%)	.87
Hemoglobin, g/dL	11.7[10.4, 13.1]	11.6 [9.5, 13.5]	11.8 [10.4, 13.2]	11.8 [10.0, 13.5]	.82
CD4 count, cells/μL	20 [8, 56]	16 [6, 51]	14 [6, 46]	11 [6, 35]	<.01
CSF Quantitative Culture, CFU/mL	87 000 [4600, 425 000]	112 000 [8000, 430 000]	43 000 [1000, 290 000]	54 000 [3000, 250 000]	.03
CSF Pressure, >25cmH_2O	191 (65%)	49 (50%)	42 (58%)	99 (61%)	.08
CSF ≥5 white cells/μL	164 (47%)	54 (51%)	34 (40%)	55 (30%)	<.001
18-week mortality	129 (37%)	44 (39%)	31 (36%)	93 (50%)	.02

Data are N (%) or median [P25,P75]. P-values from Kruskall-Wallis test for medians or Chi-square test for proportions

Figure 1. CSF Yeast Clearance rate of Early Fungicidal Activity (EFA) versus 18-week survival time. EFA < 0.20 $\log_{10}$ CFU/mL/day had decreased survival.



- There was increased 18-week mortality when EFA was <0.20 $\log_{10}$CFU/ml/day $\log_{10}$CFU/ml/day (HR = 1.6, 95%CI 1.25 – 2.04, p-0.0002).
- EFA <0.20 remained significantly associated with 18-week survival when adjusting for baseline GCS, hemoglobin, CSF QCC, CSF pleocytosis, biological sex, and cohort..

CONCLUSIONS

- EFA is independently associated with survival through 18-weeks, with increased mortality when the rate of CSF *Cryptococcus* clearance was <0.20 $\log_{10}$CFU/ml/day.
- Those with an EFA >=0.20 $\log_{10}$CFU/ml/day had a similar 18-week survival of 63% compared to 50% survival with EFA < 0.20 $\log_{10}$CFU/ml/day. Even when examining higher EFAs by further separating out he >0.40 EFA group, survival did not improve.
- Our data suggest that the target EFA for new antifungal therapies should be above 0.20 $\log_{10}$CFU/ml/day.
- Recognizing the potential prognostic feature of EFA may be an important factor when considering cessation or continuation in the early stages of phase II clinical trials.
- The short time needed to calculate a EFA, relative to other prognostic markers, can help shorten new antifungal trials.
- While we do control for many of the factors contributing to mortality in cryptococcal meningitis, EFA may not be a perfect predictor of patient outcomes as antifungal therapy along does not address all factors contributing to death.