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Efficacy And Safety Profile Of Combined Therapy Of Flucytosine And Amphotericin B In Cryptococcal Meningitis At A Tertiary Care Center In Rajasthan

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Abstract

Background: Cryptococcal meningitis (CM) from Cryptococcus neoformans or gattii can damage the brain. Although it can impact both immune-compromised and immune-competent people, its prevalence varies worldwide. Flucytosine and amphotericin B are scarce and complicated, highlighting the need for effective, accessible medicines.

Materials and Methods: This RCT examined the safety and efficacy of flucytosine and amphotericin B in treating cryptococcal meningitis in 140 Indian hospital patients from January to December 2023. The participants were divided into three equal groups and given either regular therapy, combination therapy, or no treatment.

Results: The study revealed distinct mortality patterns among the three groups. Group 1 had the highest death rates by day 14 and day 70, with 24.44% and 37.77% respectively, whereas Group 2 showed lower rates at 18.00% and 26.00%, and Group 3 at 24.44% and 26.66%. Group 2 displayed superior fungal clearance and reduced mortality risk compared to Group 1, with hazard ratios of 0.60, 0.59, and 0.49 for mortality by day 14, 70, and 182, respectively. Adverse events were prevalent across all groups, with significant variations in occurrences such as neutropenia.

Conclusion: The study has concluded that the 2-week combination treatment of flucytosine and amphotericin B reduced mortality in HIV patients with cryptococcal meningitis, showing similar results to a 1-month regimen of amphotericin B alone.

Keywords: Cryptococcal meningitis, Cerebrospinal fluid, Flucytosine, Amphotericin B

Introduction

The fungus pathogen Cryptococcus neoformans, which causes cryptococcal meningitis (CM), poses a serious threat to both vulnerable and people with normal immune systems. Patients with impaired immune function through cells, such as those with infections caused by HIV, cancers, or long-term use of immunosuppressants or steroids, are more susceptible to it. This invasive infection is extremely dangerous since it can cause vascular events in as many as 30% of patients, particularly when the illness is severe [1-2].

A serious central nervous system (CNS) risk is cryptococcal meningitis (CM), caused by infections caused by Cryptococcus neoformans or Cryptococcus gattii. Although it most frequently affects immunocompromised people. The consequences of

this illness include permanent central nervous system damage, which includes visual impairment, increased intracranial pressure, and cognitive decline. The diagnosis is based on the investigation of cerebrospinal fluid (CSF), including identifying cryptococcal antigen and culture [3-5].

The difficulties include restricted access to vital drugs, such as flucytosine and amphotericin B, which are necessary for successful induction therapy but are frequently unavailable in low-resource locations, leading to unacceptable high death rates [6]. Furthermore, there are serious toxicity hazards associated with amphotericin B use, and therapeutic limits are further compounded by the fact that flucytosine is not available in many middle-class or low-income nations [7]. The startlingly high death rates persist despite progress, highlighting the critical need for greater accessibility to safe and efficient antifungal medication that can lessen the severe effects of CM, especially in low- and middle-income nations [8-9]. The combination of flucytosine and amphotericin B has been shown to have a much higher mycologic potency against fungi than either medication alone, which is why they are used together to cure CM. Research has demonstrated the effectiveness of this combo therapy by linking it to increased rates of candida elimination from CSF and enhanced survival rates. Because of this, it is suggested that this combination be used as the first stimulation remedy for CM, highlighting its critical role in preventing the illness [10-11].

However, more thorough testing of this combined approach is necessary to fill in any discrepancies in the literature and guarantee a solid grasp of its effectiveness and safety profile. This will improve the therapy's practical applicability and patient outcomes [12-13].

This study aims to give evidence-based recommendations for the best course of treatment by examining the effectiveness and safety of a combination regimen. This investigation has the potential to greatly improve patient outcomes and lessen the financial strain associated with this serious fungal illness by filling in knowledge gaps and providing insights into better therapeutic options.

Materials And Methods

This randomized prospective controlled trial was conducted among 140 patients from January 2023 to December 2023 in our hospital in India.

This randomized controlled trial (RCT) study examined the safety and effectiveness of treating cryptococcal meningitis with a combination of flucytosine and amphotericin B. To conduct this study, the patients were randomly allotted to one of three treatment groups, namely, Group 1, Group 2, and Group 3. The patient groups were randomly assigned to three treatment groups.

1. Group 1: Intravenous amphotericin B at the dose of 1 mg/kg/day for 28 days.
2. Group 2: Intravenous amphotericin B at the dose of 1 mg/kg/day along with 100 mg/kg/day flucytosine for 2 weeks.
3. Group 3: Intravenous amphotericin B at the dose of 1 mg/kg/day along with fluconazole at a dose of 400 mg twice daily for 2 weeks.

Furthermore, the decrease in fungal load was determined by quantitative yeast counts in cerebrospinal fluid (CSF) specimens and was among of the primary outcome criteria. Again, the adverse events associated with therapy, mortality rates at specific periods, and neurological sequelae during follow-up visits were all assessed by the secondary outcomes. In contrast, healthcare providers who were charged with patient care recruited participants as well as provided them with their study treatment. Similarly, an individual from the study team monitored all inpatients every day to ensure consistent care and accurate data collection. Again, medically important lumbar punctures monitored intracranial pressure and medication efficacy weekly for the first month. Moreover, this extensive study demonstrated the efficacy and safety of combination therapy for HIV-positive cryptococcal meningitis.

Statistical Analysis

The study has used SPSS-27 for effective analysis. The continuous data were expressed as mean±SD. The discrete data were expressed as frequency and percentage. Multi-test endpoint analysis is optional, according to Schulz and Grimes. The primary analysis used data from the intention-to-treat group, which included all randomized patients. The level of significance was considered to be $P<0.05$.

Results

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Table 1 provides baseline characteristics of patients across three groups. Mean ages are relatively consistent, with Group 1 having a slightly higher mean age of 25.56 years compared to 24.78 and 25.52 years in Groups 2 and 3, respectively. Male predominance varies among groups, with Group 1 showing the highest percentage at 84.44%. Intravenous drug use is more prevalent in Groups 2 and 3 compared to Group 1. Symptoms duration, such as headache and fever, shows varying trends across groups. Neurological manifestations, including seizure and Glasgow Coma Scale scores, exhibit minor differences. Cerebrospinal fluid (CSF) parameters, such as white-cell count and glucose level, display subtle variations among groups. Plasma glucose levels and other laboratory values also demonstrate similar trends with slight variations in means and interquartile ranges across the groups.

Table 1: Baseline characters of the patients

Characteristic	Group 1(n=45)	Group 2 (n=50)	Group 3 (n=45)
Age (year)			
Mean age	25.56±4.59	24.78±4.71	25.52±3.45
Interquartile range	21-27	22-28	23-29
Male sex—no. (%)	38 (84.44%)	35 (70.00%)	32 (71.11%)
Intravenous drug use—no./total no. (%)	20/30 (66.66%)	30/35 (85.71%)	35/40 (87.50%)
Duration of symptoms—days			
Median	13	15	14
Interquartile range	6-19	8-21	7-19
Headache—no./total no. (%)	35/38 (92.10%)	32/35 (91.42%)	38/39 (97.43%)
Fever—no./total no. (%)	15/38 (39.47%)	22/35 (62.85%)	23/35 (65.71%)
Neck stiffness—no./total no. (%	11/35 (31.42%)	12/37 (32.43%)	12/34 (35.29%)
Seizure—no./total no. (%)	8/25 (32.00%)	9/26 (34.61%)	8/29 (27.58%)
Glasgow Coma Scale score—no./total no. (%)			
15	7/22 (31.81%)	8/24 (33.33%)	7/25 (28.00%)
11–14	11/26 (42.30%)	12/24 (50.00%)	13/25 (52.00%)
≤10	8/24 (33.33%)	9/25 (36.00%)	11/25 (44.00%)
Cranial–nerve palsy—no./total no. (%)	9/26 (34.61%)	10/26 (38.46%)	9/28 (32.14%)
Papilledema—no./total no. (%)	5/15 (33.33%)	6/22 (27.27%)	7/21 (28.57%)
CSF opening pressure >18 cm of CSF—no./total no. (%)	4/21 (19.04%)	3/18 (16.66%)	5/12 (41.66%)

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CSF white–cell count—cells/ml			
Mean	19.3 ± 16.8	17.6 ± 19.5	16.3 ± 18.6
Interquartile range	8-67	7-61	6-68
CSF glucose level—mmol/liter			
Mean	2.35 ± 0.56	2.42 ± 0.46	2.39 ± 0.47
Interquartile range	1.50-3.01	1.70-2.99	1.70-2.99
Plasma glucose level—mmol/liter*			
Mean	5.81 ± 0.51	5.89 ± 0.49	5.60 ± 0.46
Interquartile range	4.81-6.50	4.88-6.88	4.80-6.30
CSF yeast count—log10 CFU/m			
Mean	5.90 ± 0.40	5.75 ± 0.66	5.54 ± 0.66
Interquartile range	5.48-6.48	4.70-6.20	4.80-6.30
CD4 count—cells/mm3			
Mean	14.3 ± 9.9	13.9 ± 5.9	17.0 ± 13.1
Interquartile range	5-30	7-18	7-40
Creatinine—µmol/liter			
Mean	75.0 ± 14.2	74.7 ± 13.6	70.2 ± 9.5
Interquartile range	59.1-90.2	59.1-88.6	60.2-79.2

Table 2 presents the primary outcomes of patients across three groups. Coprimary outcomes include death rates by day 14 and day 70, with Group 1 having the highest death rate by day 14 at 24.44%, followed by Group 3 at 24.44% and Group 2 at 18.00%. However, by day 70, Group 1 maintains the highest death rate at 37.77%, while Group 2 and Group 3 show lower rates at 26.00% and 26.66% respectively. The probability of survival varies between groups, with Group 2 exhibiting the highest probability at both time points. In the per-protocol population, death rates by day 70 are similar to those of the overall population. Group 3 shows the highest remission rate of CSF fungal infection at 48.88%, while Group 1 has the lowest at 33.33%. The estimated change in CSF fungal count over the first 14 days is relatively consistent among the groups. However, Group 2 shows a higher remission rate per person-week of follow-up compared to the other groups.

"Table 2: Primary outcomes of patients across three groups"

Outcome	**Group 1(n=45)**	**Group 2 (n=50)**	**Group 3 (n=45)**
Coprimary outcomes			
Death by day 14			
No. of deaths	11 (24.44%)	9 (18.00%)	11 (24.44%)
	0.70 (0.71 to	0.80 (0.79 to 0.89	0.78 (0.70 to

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Probability of survival (95% CI)	0.80)	)	0.89)
Death by day 70			
No. of deaths	17 (37.77%)	13 (26.00%)	12 (26.66%)
Probability of survival (95% CI)	0.50 (0.49 to 0.69)	0.69 (0.60 to 0.79)	0.69 (0.59 to 0.79)
Outcomes			
Death by day 70 in the per-protocol population			
No. of deaths/no. of patients included in analysis	11/34 (32.35%)	8/34 (23.52%)	12/38 (35.29%)
Probability of survival (95% CI)	0.50 (0.49 to 0.69)	0.69 (0.60 to 0.79)	0.69 (0.69 to 0.79)
Death by day 182			
No. of deaths	24	15	26
Probability of survival (95% CI)	0.49 (0.39 to 0.59	0.70 (0.59 to 0.79)	0.49 (0.50 to 0.69)
Estimated change in CSF fungal count in first 14 days (95% CI)—log10CFU/ml/day	−0.30 (−0.30 to −0.33)	−0.40 (−0.40to −0.46)	−0.30 (−0.30 to −0.32)
CSF fungal remitted			
No. of patients whose fungal infection was remitted	15 (33.33%)	13 (26.00%)	22 (48.88%)
Remission rate per person-wk of follow-up (95% CI)	0.14 (0.10 to 0.18)	0.27 (0.28 to 0.50)	0.24 (0.18 to 0.32)

Figure 1 depicts Kaplan–Meier survival estimates for each group over time. At day 0, all groups start with 99-100 individuals. By day 182, Group 1 has the lowest number of survivors at 30, followed by Group 3 with 39 survivors, and Group 2 with 46 survivors. The survival curves for Groups 1 and 3 decline more rapidly compared to Group 2, indicating higher mortality rates over time. The p-value of 0.0425 suggests that there is a statistically significant difference in survival among the three groups. This difference indicates that the probability of survival varies significantly between the groups throughout the observation period.

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"Figure 1: Kaplan–Meier survival estimates for each group; P=0.0425"

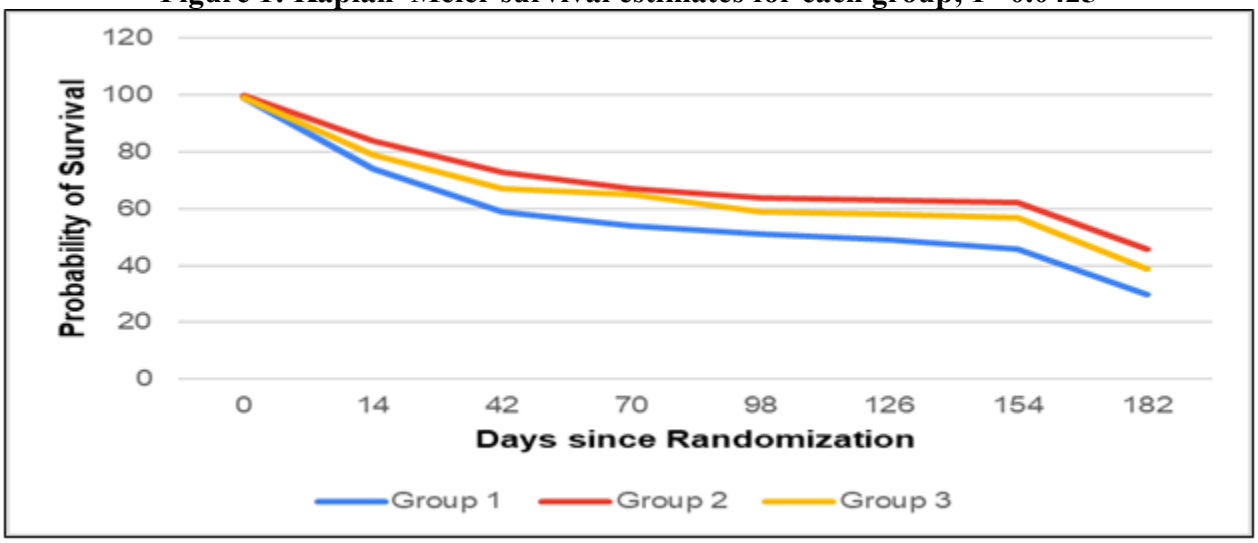

Table 3 shows hazard ratios or estimated change differences with 95% confidence intervals (CI) for various outcomes for different treatment groups in the study. The hazard ratios for death by day 14, 70, and 182 are: Group 2 vs. Group 1, Group 3 vs. Group 1, and Group 2 vs. Group 3. A hazard ratio below 1 indicates a lower death risk in the cited group than in the comparator group.

Comparing Group 2 to Group 1, the hazard ratios for mortality by day 14, 70, and 182 are 0.60, 0.59, and 0.49, respectively. These ratios indicate that Group 2 has a lower death risk than Group 1 at each time point. We estimate the change in CSF fungal count during the first 14 days of treatment for each group. Negative changes indicate fungal decline over time. Comparing Group 2 to Group 1, the estimated CSF fungal count change is -0.09 (log10CFU/ml/day), with a 95% CI of -0.09 to -0.08. In the first 14 days of treatment, Group 2 had a significantly lower fungal count than Group 1. The hazard ratios for CSF fungal clearance show the likelihood of clearance in each therapy group. Comparing Group 2 to Group 1, the CSF fungal clearance hazard ratio is 3.11, with a 95% CI of 2.09 to 4.59. The likelihood of CSF fungal clearance in Group 2 is considerably greater than in Group 1.

"Table 3: Secondary outcomes of three groups"

	Group 2 vs. Group 1	P Value	Group 3 vs. Group 1	P Value	Group2 vs. Group 3	P Value
Death by day 14	0.60 (0.29 to 1.11)	0.07	0.69 (0.39 to 1.39)	0.39	0.69 (0.29 to 1.39)	0.38
Death by day 70	0.59 (0.40 to 0.88)	0.03	0.69 (0.39 to 1.09)	0.09	0.91 (0.49 to 1.39)	0.49
Death by day 70 in the per-protocol population	0.59 (0.40 to 0.88)	0.03	0.70 (0.39.to 1.09)	0.1	0.82 (0.519 to 1.49)	0.7
Death by day 182	0.49 (0.41 to 0.91)	0.02	0.81 (0.49 to 1.09)	0.19	0.69 (0.459 to 1.09)	0.11

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Estimated change in CSF fungal count in first 14 days (95% CI)— log10CFU/ml/day	−0.09 (−0.09 to −0.08)	<0.001	0.00 (−0.03 to 0.05)	0.79	−0.09 (−0.09 to −0.08)	<0.001
CSF fungal clearance	3.11 (2.09 to 4.59)	<0.001	1.41 (0.88 to 2.11)	0.09	2.31 (1.588 to 3.30	<0:001

Table 4 presents an extensive overview of adverse events across three groups, indicating the prevalence and statistical significance of each event. Firstly, the table reveals that a considerable proportion of patients in all groups experienced at least one adverse event, with percentages ranging from 70.00% to 77.77%. However, the p-value of 0.79 suggests no significant difference in the overall occurrence of adverse events among the groups. Examining specific adverse events, hypokalemia was observed in 44.44% of Group 1 patients, 32.00% of Group 2, and 31.11% of Group 3. Despite variations, the p-value of 0.88 indicates no statistically significant difference in hypokalemia incidence among the groups. Similarly, while neutropenia rates differed across groups (15.55% in Group 1, 24.00% in Group 2, and 22.22% in Group 3), the associated p-value of 0.03 suggests a significant variation. In contrast, events like thrombocytopenia and seizures did not demonstrate significant differences in occurrence among the groups, with p-values of 0.29 and 0.4, respectively. These findings highlight the diverse adverse event profiles among the groups, with some events showing notable discrepancies while others display more consistent distributions. Such insights contribute to understanding the safety profiles of interventions and guiding clinical decision- making.

"Table 4: Overview of adverse events among three groups"

Event	**Group 1(n=45)**	**Group 2 (n=50)**	**Group 3 (n=45)**	**P-value**
Any event				
At least one event — no. of patients (%)	34 (75.55%)	35 (70.00%)	35 (77.77%)	0.79
No. of events	321	359	369	
Hypokalemia — no. of patients (%)				
All grades	20 (44.44%)	16 (32.00%)	14 (31.11%)	0.88
Anemia — no. of patients (%)				
All grades	26 (57.77%)	23 (46.00%)	17 (37.77%)	0.59
Neutropenia — no. of patients (%)				

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All grades	7 (15.55%)	12 (24.00%)	10 (22.22%)	0.03
Thrombocytopenia — no. of patients (%)				
All grades	3 (6.66%)	5 (10.00%)	4 (8.88%)	0.29
Rigor — no. of patients (%)	4 (8.88%)	3 (6.00%)	3 (6.66%)	0.15
Opportunistic infection — no. of patients (%)	8 (17.77%)	9 (18.00%)	7 (15.55%)	0.81
Rash — no. of patients (%)	2 (4.44%)	3 (6.00%)	4 (8.88%)	0.89
New neurologic sign or symptom — no. of patients (%)	5 (11.11%)	4 (8.00%)	3 (6.66%)	0.97
Seizure — no. of patients (%)	1 (2.22%)	0	1 (2.22%)	0.4
Elevated aminotransferase level — no. of patients (%)				
All grades	12 (26.66%)	13 (26.00%)	13 (28.88%)	0.69
Hyponatremia — no. of patients (%)				
All grades	11 (24.44%)	12 (24.00%)	13 (28.88%)	0.69
Hypercreatinemia — no. of patients (%)				
All grades	11 (24.44%)	10 (20.00%)	12 (26.66%)	0.19
Other — no. of patients (%)	5 (11.11%)	4 (8.00%)	3 (6.66%)	0.39

Discussion

Adherence to the protocol was noted in therapy in the comparison between amphotericin B therapy and a more recent regimen combining both medications for CM as studied by Bennett et al. (1979). Of these, the combined regimen and amphotericin B alone. Even though the combined regimen took six weeks instead of ten for amphotericin B alone, more patients exhibited improvement or cure, and the combination therapy resulted in fewer unsuccessful attempts or recurrent episodes (three vs. Eleven). In comparison to amphotericin B alone, the combination regimen also showed faster sterilization of CSF fluid and reduced nephrotoxicity. Flucytosine adverse reactions were

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noted to occur in eleven out but did not present a risk to the lives of thirty-four patients. For CM, the combination is therefore considered the best course of action [14].

Another study by Nguyen et al. (1995) showed that combination worked synergistically in most cases, and that flucytosine's cellular inhibiting capability was enhanced [15]. Furthermore, results from a placebo-controlled study by Day et al. (2013) showed that amphotericin B with flucytosine was related to improved outcomes amongst those suffering from CM [16]. Eighteen consecutive patients were included in a trial to assess the effectiveness and tolerance of main treatments for CM in individuals with HIV in a study by Jaruratanasirikul S (1996). For two weeks, they received amphotericin B injected with or without flucytosine. After that, they took fluconazole orally for eight weeks. Following treatment, oral fluconazole was administered as a maintenance dose to each patient. Ninety-four percent of patients responded well to primary therapy, and it took an average of three weeks for the initial abnormal CSF cultures for fungi. Adverse medication reactions did not result in treatment discontinuations, and no cases of relapse were reported during the monitoring period. When used as the main treatment, these results imply that the regimen is both efficacious and well-tolerated [17].

The effectiveness and safety of combination therapy in treating CM have been well studied. Together, these studies highlight this therapy regimen's significant therapeutic benefits. In particular, studies have shown a high overall success rate in treating CM, indicating that the treatment helps eradicate the infection and enhance patient outcomes. Additionally, analysis has shown mortality rates, which are important markers of both therapy efficacy and overall longevity of patients. Furthermore, research has demonstrated improved survival rates for individuals undergoing combination therapy, highlighting the treatment's capacity to extend life expectancy and lessen the severity of the illness [18].

Additionally, evaluations have shown elevated yeast clearance from CSF fluid, indicating the effectiveness of the treatment in eliminating the fungal infection from the CNS. It is vital to acknowledge the manifestation of unfavorable consequences linked to this therapy methodology. Adverse events were noted in all dosage groups, despite the treatment's overall effectiveness. This highlights the necessity of close observation and prompt care of any possible side effects to guarantee safeguards for patients and treatment compliance [19].

It is commonly known that combination therapy effectively treats CM. Research has indicated that this treatment regimen produces better patient outcomes than monotherapy, as seen by increased rates of remission or recovery and decreased rates of unsuccessful therapy or relapse. Furthermore, the combined medication has demonstrated good tolerability characteristics, including less nephrotoxicity and improved clearance of yeast from the cerebrospinal fluid. However, flucytosine's propensity for severe toxicity highlights how crucial it is to monitor and manage patients carefully to guarantee patient safety. Consequently, the administration of a combination regimen necessitates thorough evaluation and tolerance monitoring [20-22].

The study's conclusions have major therapeutic ramifications since they indicate that the best induction therapy for CM is combination therapy, particularly when it includes amphotericin B and flucytosine. This treatment strategy has shown improved survival rates and accelerated removal of the pathogenic fungi from the CSF. These implications are especially significant for clinical practice since they support the use of flucytosine and amphotericin B as the main induction therapies for CM, especially in resource- constrained settings. These discoveries could lead to changes in recommended courses of care, emphasizing how important it is to use combination therapy to improve patient outcomes [18].

Subsequent investigations into the therapy of CM may concentrate on several important areas. First, efforts might be focused on improving treatment plans by adjusting antifungal medication concentrations, time frames, and combos to maximize effectiveness and minimize side effects. Second, research into novel compounds or alternate combination therapy may be able to address the drawbacks of the pharmacological treatments already in use, such as their high rates of resistance and toxicity. Furthermore, studies could examine the advantages of using adjuvant medications, including steroids or synthetic interferon-g, in addition to regular treatment methods. Furthermore, improving the availability of necessary antifungal medications, especially in low- and middle-

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income nations, may have a substantial effect on the state of world health. Finally, studying the immune-mediated cause of CM by examining samples of CSF may provide important new information in understanding the course of the disease and make it easier to find biomarkers for improved clinical care [12, 9, 23].

Conclusion

The study has concluded that the 2-week combination treatment of flucytosine and amphotericin B reduced mortality in HIV patients with cryptococcal meningitis, showing similar results to a 1-month treatment of amphotericin B alone and combination with fluconazole at a dose of 400 mg twice daily for 2 weeks. The use of fluconazole in combination therapy for two weeks did not appear to be beneficial. Research into innovative drug delivery systems or formulations to increase medicine accessibility and delivery could enhance cryptococcal meningitis treatment adherence and results. Antifungal resistance mechanisms must be studied, and measures developed to reduce resistance for existing and future treatment methods to work.

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