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Efficacy of liposomal amphotericin B in treating fungal meningitis in AIDS Patients: A review article

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Abstract

Cryptococcal meningitis is an alarming fungal infection that usually affects the meninges surrounding the brain and spinal cord. The causative organism is *Cryptococcus neoformans*. Although this infection can occur in normal individuals, it is more often seen in patients with human immunodeficiency virus/acquired immunodeficiency syndrome. Amphotericin B is an antifungal medication often used to treat severe fungal infections. It belongs to the class of polyene antifungal drugs, and it acts by binding to the cell membrane of the fungus. This causes some essential cellular components to leak out and ultimately the fungus dies. However, the administration of Amphotericin B is associated with toxicity. Therefore, lipid formulations are preferred to decrease the toxicity and increase the therapeutic index of the drug. It is widely used since it has a longer tissue half-life, the drug induced toxic effects are lower and it can penetrate the brain tissue efficaciously. This review collects and analyzes several research studies and literature reviews found in the electronic databases. The inclusion criteria prioritize studies focusing on the efficacy and drawbacks of using liposomal Amphotericin B as a treatment for fungal meningitis. In conclusion, liposomal Amphotericin B showed more effective treatment compared to other available antifungal drugs. Patients treated with a single dose of liposomal Amphotericin B coupled with fluconazole and flucytosine exhibited fewer adverse events and the mortality rate was also lower as compared to the control group.

Keywords: Cryptococcal Meningitis, Fungal Meningitis, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome, Amphotericin B, Liposomal Amphotericin B, Antifungal Drugs

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Introduction

Fungal meningitis is one of the most severe complications seen in patients with acquired immunodeficiency syndrome (AIDS), specifically those receiving improper treatment or having advanced human immunodeficiency virus (HIV)/AIDS. Common pathogens causing fungal

meningitis include *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides* spp., *Aspergillus* spp., and other opportunistic fungi.[1] Cryptococcal meningitis, caused by *C. neoformans* is typical of fungal meningitis seen in HIV/AIDS patients. Additionally, it stands out as the most prevalent systemic fungal infection among individuals with HIV and is the primary cause of meningitis.[2] In the Western World, around 5% of HIV-infected patients develop disseminated cryptococcosis. However, higher rates are observed in regions like sub-Saharan Africa and Thailand (20-30%). *C. neoformans*, a soil organism, is an encapsulated yeast with two serologically distinguishable varieties - *C. neoformans* var. *neoformans* (serotypes A and D) and *C. neoformans* var. *gatti* (serotypes B and C).[3] Nearly all HIV-associated infections are attributed to *C. neoformans* var. *neoformans*.

The speculated initial infection occurs through inhalation of basidiospores or unencapsulated forms, leading to airway colonization and subsequent respiratory infection. Pulmonary macrophages play a crucial role in yeast control, with complement-mediated phagocytosis serving as the primary defense against cryptococcal invasion.[4] Other host-yeast interactions involving cluster of differentiation CD4+ and CD8+ T-cells, along with cytokines such as gamma interferon, tumor necrosis factor alpha, interleukin 10 (IL-10), and 1L-12, also contribute to immune response. Murine models suggest that both CD4+ and CD8+ T-cells are necessary to inhibit cryptococcosis, and cytokines are essential in limiting dissemination. Consequently, the compromised cell-mediated immunity in progressive HIV infection significantly increases the risk of disseminated cryptococcal infection. The role of humoral immunity in controlling cryptococcal infections is less certain.[5]

A recent case-control study indicated an association between reduced expression of specific immunoglobulin subsets and cryptococcal meningitis in HIV-infected patients. In vitro studies of antibodies to the soluble capsular polysaccharide of *C. neoformans* reveal enhanced phagocytosis, increased fungicidal activity of leukocytes, and heightened fungistatic activity of natural killer cells.[6] Infection with HIV makes an individual more prone to getting infected with fungal meningitis due to risk factors such as low CD4 cell count, increased susceptibility to opportunistic infections, non-adherence to antiretroviral therapy (ART) adherence, lack of primary prophylaxis and co-existing conditions which further weaken the immune system.

The duration of symptoms and signs from onset to clinical presentation is usually 1 to 2 weeks in HIV cases and 6 to 12 weeks (about 3 months) in non-HIV cases. The case generally presents neurological symptoms like a headache and altered internal status. Symptoms include languor along with fever, stiff neck, nausea and vomiting. Some cases who are HIV positive may have minimum or nonspecific symptoms. Visual symptoms include diplopia and photophobia at the onset, and reduced perceptivity later in the illness due to high cerebrospinal fluid (CSF) pressure or compression of the optic nerve and tracts. Other findings include hearing blights, ataxia, aphasia, seizures, and chorea.[7]

Treatment generally involves antifungal medications, most commonly Amphotericin B (AmB) and flucytosine, followed by maintenance therapy with fluconazole. However, successful treatment can be challenging, especially in patients with advanced HIV/AIDS or those who have difficulty tolerating medications due to side effects or drug interactions. The aim of this article is to compare between AmB and liposomal amphotericin B (LAmB) to find out which one is the most effective against fungal meningitis specifically in AIDS patients and thereby aim to help in decision making when selecting the most appropriate treatment options.[8,9]

Materials and Methods

Electronic databases including PubMed/Midline, Web of Science, and Google Scholar were searched for case reports and series, case control, cohort, and cross-sectional studies, and reviews from the database's inception to January 2024. The inclusion criteria included studies written in English and relevant to our objectives, without any restrictions regarding time, population category, and/or detection

assay. The terms used to search articles included “Cryptococcal Meningitis”, “Antifungal Drugs”, “Amphotericin B”, “Liposomal Amphotericin B”, “Efficacy” and so on.

Antifungal Drugs

The treatment of fungal meningitis is usually begun with a long course of antifungals administered intravenously, followed by oral antifungals. While there are several antifungals, the type and dosage depend on the health status of the patient, and whether they suffer from other conditions such as AIDS/HIV.

1. Azoles

Azoles belong to a class of antifungal drugs that function by inhibiting the synthesis of ergosterol, an essential component of the fungal cell membranes. These are effective against a wide range of fungal species including yeast and mold. They work by inhibiting lanosterol 14 alpha demethylase, an important enzyme for the conversion of lanosterol to ergosterol.[10] Without ergosterol, the fungal cell membrane becomes unstable and leaky which leads to death of the fungal cell. Azoles can be classified into two main classes: Imidazoles and Triazoles. Imidazoles, is used topically for superficial fungal infections, including ketoconazole, miconazole, clotrimazole and econazole. Triazoles include fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole.[11] They are available in both oral and intravenous formulations. In 2002, voriconazole was approved to treat serious fungal infections, while posaconazole was licensed in 2006. These drugs are considered safer and have lesser toxic effects compared to AmB which belongs to a class of polyenes and flucytosine.[12]Azoles are often the first-line options for prophylaxis of invasive fungal infections. The chronic use of azoles is usually associated with hepatic toxicity and several hormone related effects such as alopecia, oligospermia, impotence, hypokalemia, hyponatremia and gynecomastia. The newer azoles, voriconazole and posaconazole have been linked to peripheral neuropathies, whereas itraconazole and voriconazole have been associated with pancreatitis.[13,14]

Fluconazole, in dosages ranging from 400 mg weekly to 200 mg daily, and itraconazole, 100 mg twice daily, are very effective in preventing invasive cryptococcal infections, especially in HIV-positive patients with CD4 counts < 50-100 cells/mm3. However, because of the relative infrequency of invasive fungal infections, antifungal prophylaxis does not prolong life and is not routinely recommended.[15]

2. Echinocandins

Echinocandins act by inhibiting the enzyme β-(1,3)-d-glucan synthase, which is essential for the synthesis of integral cell wall components of several fungi.[16] These drugs work effectively against *Aspergillus* spp. and most *Candida* species including strains that are fluconazole resistant. Three echinocandin antifungal agents are currently approved for use in the United Sates of America (USA): caspofungin, micafungin, and anidulafungin.[17]

3. Flucytosine

Flucytosine is an oral antifungal that has activity against most *Candida* spp. The primary rates of resistance for *C. neoformans* against flucytosine range between 1% and 24.5%.[18] Due to the development of rapid primary and secondary resistance, it is rarely used as a monotherapy and limited to selected cases of candidal cystitis/pyelonephritis. However, combination therapy of flucytosine with AmB has been proven to improve treatment outcomes in patients with cryptococcal meningitis. Moreover, there are other concerns regarding the use of flucytosine namely lack of parenteral preparation, hematological toxicity and high cost.[19,20]

4. Griseofulvin

Griseofulvin is an antifungal medication produced by ascomycetes (sac fungi). Since its introduction in 1959, it has been used to treat various dermatophyte infections.[21] It acts by binding to tubulin, which is an important structure involved in mitosis. After binding to tubulin, it causes disruption of microtubules, thereby interfering with the formation of mitotic spindle. Due to this inhibition the fungal cell is not able to divide and proliferate, leading ultimately to inhibition of the fungal growth.[22]

However, the drug comes with quite a few side effects including gastrointestinal disturbances, skin reactions, photosensitivity, and various allergic reactions.[23]

Amphotericin B and Liposomal Amphotericin B

1. Mode Of Action

In fungi, AmB interacts with ergosterol in the fungal cell membrane, resulting in the creation of pores, ion leakage, and eventual cell death.[24] In vitro and in vivo assays revealed that both fluorescently labeled liposomes and gold-labeled liposomes demonstrated the binding of liposomes (both loaded with AmB and empty) to the cell wall of pathogenic yeasts and molds.[25] In these experiments, liposomes lacking AmB showed binding to the fungal cell wall, but both the empty liposomes and the fungal cell remained intact. In contrast, when AmB containing liposomes were bound, it led to fungal cell death, indicating that binding causes liposomal disruption and the release of AmB.[26] The released AmB is then free to exhibit its fungicidal effects by binding to ergosterol in the fungal cell membrane.[27] The specific mechanism by which AmB is transferred from the liposome through the fungal cell wall to the fungal membrane is not fully understood. It is probable that this process is facilitated by the higher affinity of AmB for ergosterol (the primary sterol in fungal cell membranes) compared to cholesterol, the primary lipid component of the liposome.[28] Moreover, temperature seems to play a crucial role in the efficient transfer of AmB between the liposome and the fungus, with the process being most effective at normal body temperature.[29]

2. Pharmacokinetics

The pharmacokinetics of AmB exhibit variations across different species. Following intravenous (IV) administration, AmB predominantly binds to lipoproteins, albumin, and erythrocytes.[30] Due to its limited solubility, the concentration of free AmB in the bloodstream remains below 1 mg/l. After IV administration, the peak serum concentrations are reached within the first hour, followed by a rapid decline to a plateau phase lasting approximately 24 hours, and succeeded by a more extended terminal elimination phase that spans several days. This latter phase is likely an explanation of the gradual release of AmB from tissues.[31]

In animal models, AmB attains its highest concentrations in organs such as the liver, spleen, lungs, and kidneys.[32] The concentrations of AmB in uninflamed meninges are markedly lower than concurrent serum levels, with minimal presence in CSF. However, higher AmB concentrations are observed in the brain parenchyma, demonstrating persistent antifungal effects.[33] Notably, LAmB outperforms conventional AmB in terms of brain tissue concentrations, especially in cases of experimental *Candida* meningoencephalitis.[34]

The administration of AmB by IV does not penetrate the uninflamed eye, but when inflammation is present, higher levels of LAmB are detected in both the aqueous and vitreous humor compared to AmB.[35] LAmB, due to its stability after IV injection and small particle size, exhibits enhanced tissue penetration. This penetration is observed in various tissues, both in uninfected and infected animal models, with liposomes localizing at sites of fungal infection in the lungs, liver, spleen, kidneys, and brain.[36] The size of the liposomes (less than 100 nm) allows them to initially bypass uptake by macrophages in the reticuloendothelial system tissues. Subsequently, over a 24-hour period, circulating liposomes are gradually taken up by macrophages, concentrating primarily in the liver and spleen.[37] The nonlinear increase in drug concentration with increasing LAmB dosage is particularly noteworthy when administering the drug daily for an extended duration. Overall, LAmB concentrations in animal tissues is most prominent in liver and spleen which is significantly more than that in the kidneys followed by lungs and lastly the brain, with levels surpassing the minimum inhibitory concentration for most fungi.[38] Preclinical studies indicate varying clearance times for LAmB from different organs, ranging from approximately 1 day for the brain, a few days for the lungs, to several weeks for the kidneys, spleen, and liver.[39]

3. Formulations of Liposomal Amphotericin B.

Research aimed at enhancing the conventional AmB focused on combining it with lipid carriers like cholesteryl sulfate, phosphatidyl choline, or phosphatidyl glycerol.[40] This led to the development of three lipid-based forms: the AmB cholesteryl sulfate complex, the AmB lipid complex, and LAmB.[41] Traditional AmB formulations faced solubility challenges in water. Consequently, standard parenteral amphotericin products use deoxycholic acid to establish a stable colloidal dispersion.[42] The AmB lipid complex, involves a combination of AmB with phosphatidyl choline and phosphatidyl glycerol. Particles in this complex vary in size from 1,600 nm to 11,000 nm and exhibit a "ribbon-like" shape.[43] AmB cholesteryl sulfate complex is a formulation combining AmB with cholesteryl sulfate. Particles in this complex range in size from 120 nm to 140 nm and are described as "disk-shaped".[44] LAmb, comprises small, single-layer vesicular particles measuring 60 nm to 70 nm. These particles are composed of hydrogenated soy phosphatidyl choline and distearoyl phosphatidylglycerol, stabilized by cholesterol and amphotericin B.[46] The different formulations of AmB are summarized in Table 1.

Table 1. Composition of lipid formulation of amphotericin B. [41,42,45]

Formulation of amphotericin B	Composition
Amphotericin B cholesteryl sulfate complex	AmB with cholesteryl sulfate.
Amphotericin B lipid complex	AmB with phosphatidyl choline and phosphatidyl glycerol.
Liposomal amphotericin B	Hydrogenated soy phosphatidyl choline and distearoyl phosphatidylglycerol, stabilized by cholesterol and AmB.

4. Side effects

LAmB has significantly improved the treatment of invasive fungal infections. However, like any medication, it is associated with potential side effects.[44] One of the common side effects of LAmB is infusion-related reactions. These reactions, occur during or shortly after the administration of the drug, may manifest as fever, chills, nausea, vomiting, headache, and muscle pain.[47] These can be managed by pretreatment with acetaminophen, nonsteroidal anti-inflammatory agents with or without antihistamines, and, if necessary, corticosteroids.[48] While LAmB is considered lower nephrotoxicity than AmB formulations, it can still impact kidney function. Renal function should be closely monitored during treatment, particularly in patients with pre-existing renal comorbidities.[49] Hematological effects, including anemia, leukopenia, and thrombocytopenia, are potential side effects of LAmB. Regular monitoring of blood cell counts is recommended to detect and manage these side effects.[50] Disturbances in electrolyte balance, such as hypokalemia and hypomagnesemia, can occur with LAmB treatment. Adequate monitoring and supplementation of electrolytes are crucial to prevent complications related to these imbalances.[51] Transient elevations in liver enzyme levels may be observed in some patients receiving LAmB. Regular liver function tests can help monitor hepatic function and detect any abnormalities.[52] Localized reactions at the injection site, such as pain or inflammation, may occur. Proper administration techniques, including site rotation, can help minimize these local side effects.[53]

Allergic reactions, including rash, itching, and swelling, are potential side effects of LAmB. While severe allergic reactions are rare, prompt medical attention is necessary if any signs of allergy develop.[54] In rare cases, LAmB has been associated with respiratory distress or difficulty breathing.[55]

Effectiveness of Liposomal Amphotericin B in Fungal Meningitis

LAmb is considered as the most effective option for treatment of fungal meningitis. The advantages of LAmb over AmB were studied in recent times and found that LAmb exhibited the following. It is effective against a wide range of species including *Candida*, *Aspergillus* and *Cryptococcus* species. Toxicity, specifically

nephrotoxicity, is a common concern with AmB but LAmb with its lipid formulation has made it possible to reduce the toxicity. The lipid formulation also tends to penetrate better to the blood brain barrier making it more effective in treating infections of the central nervous system. The mode of action of LAmb is mainly dependent on the presence of AmB in the liposome bilayer, chemical composition of liposome and the binding affinity to the fungal cell wall. The presence of cholesterol in the liposome layer helps in binding with AmB which keeps the AmB bound to the liposome rather than causing toxicity.[56]

While LAmb is considered to be safer than the conventional AmB, it is essential to acknowledge that no antifungal medication comes without potential side effects. It is very critical to keep a proper check on the doses of LAmb that one is intaking. A study conducted by Takazono et al., 2022, showed that combination of LAmb with flucytosine was more effective in treatment of cryptococcal meningitis in patients with HIV as compared to LAmb alone.[57] In another study conducted by Ran et al., 2019, it was reported that the treatment with LAmb in combination with flucytosine exhibited the highest survival rate as compared to treatment with AmB in combination with flucytosine.[58] In a study conducted in low- and middle-income countries it was also found that pre-emptive treatment with LAmb was more cost-effective as compared to fluconazole pre-emptive treatment.[59]

Limitations And Challenges of Liposomal Amphotericin B

LAmB represents a significant breakthrough in the management of invasive fungal infections. However, like any therapeutic agent, it is accompanied by its limitations and challenges.[60]

A significant challenge associated with therapeutic usage of LAmB is its considerably high cost as mentioned in table 2. This elevated cost can create financial barriers, hindering accessibility for both patients and healthcare systems, particularly in resource-limited settings.[61] The economic considerations of employing LAmB must be carefully evaluated against its clinical benefits.[62] LAmB is predominantly administered by IV injection. The necessity for medical supervision and suitable facilities restricts its use in outpatient settings.[63] This limitation is significant in countries where healthcare infrastructure is underdeveloped. Exploring alternative administration routes or formulations could potentially help in making the treatment more accessible.[64]

While LAmB is linked to lower nephrotoxicity compared to its conventional counterpart, there remains a risk of kidney toxicity.[65] Monitoring renal function is imperative during treatment. Ongoing research focuses on further minimizing nephrotoxicity thereby contributing to enhancing the overall safety profile of the drug.[66] The administration of LAmB can induce infusion-related reactions, including fever, chills, and rigor. These reactions may pose challenges in terms of patient acceptance of the treatment.[67] Pre-medication strategies with antipyretics and antihistamines are commonly employed to mitigate these reactions. However, ongoing research aims to discover novel methods to minimize infusion-related events.[68] While LAmB is effective against a broad spectrum of fungi, it may not cover all fungal pathogens. Some fungal species may exhibit resistance or reduced susceptibility to the drug.[69] Fungal pathogens can adapt and develop resistance over time, potentially compromising the efficacy of this antifungal therapy.[70]

Liposomal formulations often impose specific storage and stability requirements. Ensuring proper conditions, maintained throughout the drug's storage time is crucial to preserve its functioning efficacy. This is particularly a challenge in underdeveloped nations with limited infrastructural facilities. Research into formulations that are stable and maintain efficacy and stability under simple storage conditions could effectively address this limitation.[71] In contrast to some antifungal agents available in oral formulations, LAmB lacks an oral version. This limitation can adversely impact patient preference and adherence to treatment. Oral formulations are generally more convenient for patients and may facilitate outpatient management.[72] Despite the widespread clinical use of LAmB, significant research gaps persist concerning optimal

dosing, treatment duration, and long-term safety profiles. Further studies are required to lay out specific administration and treatment protocols, especially in specific patient populations such as those with compromised renal function or other comorbidities.[73]

While LAmB has revolutionized the treatment of invasive fungal infections, it has its own specific set of challenges and limitations summarized in Figure 1. Addressing these concerns requires more research, technological innovations, and careful consideration of pros and cons to define the delicate balance between clinical benefits and economic considerations.[74]

Figure 1. Limitations of Liposomal Amphotericin B.[71,72,73]

Table 2. High costs of different formulations of amphotericin B. [74]

Formulation of amphotericin B	Cost per 50 mg
Amphotericin B deoxycholate (standard formulation)	$5.06
Amphotericin B lipid complex	$86.67
Amphotericin B cholesteryl sulphate complex	$93.33
Liposomal amphotericin B	$196.25

Comparing Liposomal Amphotericin B to the conventional Amphotericin B in terms of efficacy and side effects (Advantages)

1. Reduced nephrotoxicity

Current data point to that LAmB is less nephrotoxic than traditional AmB (where the impact on renal function is quantified as a rise in blood creatinine level, at least two times higher than the initial level).[75,76] In a pilot pharmacokinetics study, the effectiveness of LAmB in treating cryptococcal meningitis in HIV/AIDS patients was investigated in India. The study found that the liposomal formulation of AmB significantly reduces side effects, such as nephrotoxicity, and safety and effectiveness in treating these patients.[77] Another study, looked at renal toxicity, found that the lipid-associated formulations were much less nephrotoxic than AmB.[78].

2. Increased Amphotericin B concentrations

LAmB escapes identification and absorption by the mononuclear phagocyte system due to its small size and negative charge. As a result, compared to traditional AmB, a single dose of LAmB produces a substantially greater peak plasma level (Cmax) and a bigger area under the concentration–time curve. Patients on LAmB often have tissue concentrations that are highest in the liver and spleen and much lower in the kidneys and lungs. The recommended daily dosages for therapy are 3–6 mg/kg.[79] Significantly greater mean blood concentrations were obtained with both doses of LAmB at weeks 1 and 2, according to the study by Hamill et al., 2010. By week two, CSF samples from just 6 patients showed detectable levels of AmB. The patients were divided into three groups on the basis of the type of treatment they received. The first group received AmB at 0.7 mg/kg/day, the second group LAmB at 3 mg/kg/day, and the third group LAmB at 6 mg/kg/day. Some individuals in all three groups still had detectable serum levels of AmB by week 10. [75]

3. Decreased infusion related reactions

A meta-analysis study contrasting LAmB and AmB, revealed a statistically significant reduction in all infusion-related side effects, including fever, chills and/or rigors, nausea, and vomiting, in the liposomal group as opposed to the traditional group.[76] The study by Hamil et al., 2010, came to the same conclusion, also noting that the LAmB 3 arm of the study saw a

lower incidence of significant anemia, as defined by a hemoglobin concentration of 8 g/dL.[75]

4. Efficacy and mortality

For those patients with AIDS and acute cryptococcal meningitis, liposomal formulation offers an equally effective substitute to the traditional formulations.[75,77] According to the study by Hamill et al.,2010, at ten weeks, the total mortality rate was 11.6%, and there were no significant differences between the three therapy groups defined above. However, according to a prior meta-analysis study, lipid-based formulations considerably lowered the risk of death by an estimated 28% when compared to traditional AmB.[79]

Safety and tolerability of liposomal amphotericin B in treating fungal meningitis in AIDS patients

Cryptococcal meningitis still accounts for 15% of fatalities in individuals with AIDS.[80] The recommended treatment for cryptococcal meningitis involves a 2-week induction therapy using AmB in conjunction with either flucytosine or fluconazole. However, flucytosine is not easily accessible in developing nations, and the limited use of AmB in resource-limited settings is due to the need for extended hospital stays and close monitoring of renal and electrolyte functions.[81] Shortening the treatment duration to one week could significantly enhance the practicality of the therapy in resource-poor environments.[81] This is because AmB's nephrotoxic effects primarily occur in the second week of treatment, and the risk of severe renal toxicity is minimal when the treatment is shortened to 7 days or less.[82,83] The findings suggest that administering intrathecal LAmB could potentially shorten AmB treatment to one week without an associated increase in mortality.[84] Prior research has indicated that the use of intrathecal AmB is poorly tolerated, with common adverse events such as leg pain, vomiting, prostration, or altered mental status.[85] However, in a study, cryptococcal meningitis patients who received intrathecal LAmB experienced mild and transient adverse events.[82] Clinical trials are necessary to validate the survival benefits of intrathecal LAmB administration in cryptococcal meningitis patients.[86]

Another study, in patients from a prospective HIV cohort study in India, conducted to compare the standard two-week therapy including one week of intravenous AmB and intrathecal AmB lipid emulsion (AmB-IL), both regimens accompanied by oral fluconazole for two weeks. It was found that the use of one week of IV AmB with AmB-IL resulted in lower costs of drugs, reduced risk of mortality and lesser hospital admission days. [84] In contrast to prior encounters with intrathecal AmB, the intrathecal administration of AmB-IL was notably well-tolerated, with only one patient experiencing transient urinary retention.[86,87] This aligns with case reports of patients receiving other lipid forms of intrathecal AmB and consistent with findings from studies involving animal models.[88,89] A preceding study conducted in mice demonstrated that a combination therapy involving intrathecal LAmB and fluconazole effectively reduced mortality compared to intravenous LAmB monotherapy.[90] Furthermore, mice treated with intrathecal LAmB exhibited minimal inflammatory signs in the meninges.[91]

Discussion

The studies mentioned in Table 3 offer a valuable insight into the efficacy and safety of LAmB in the treatment of cryptococcal meningitis, particularly in patients with AIDS and other immuno-compromised conditions. These studies collectively mention the effectiveness of LAmB in treating cryptococcal meningitis.[92,93,94] LAmB offers several advantages over conventional AmB formulations, including reduced nephrotoxicity and infusion-related adverse effects. The study by Jadhav et al., 2010, demonstrated that a higher dose of LAmB (3 mg/kg/day) is more efficacious than a lower dose (1 mg/kg/day), resulting in quicker microbial conversion of CSF and shorter treatment duration.[93]This finding suggests that elevating the dosage can lead to improved clinical outcomes. Similarly, the study by Hamill et al., 2010, found that LAmB is as efficacious as conventional AmB in treating

cryptococcal meningitis in AIDS patients.[75] Moreover, liposomal formulations showed significantly lower rates of infusion-related reactions and nephrotoxicity, enhancing its safety profile compared to conventional formulations.

The studies conducted by Torre et al., 1998, and Hamill et al., 2010, provide valuable insights into the comparative effectiveness of LAmB versus conventional formulations.[75, 92] While the study by Torre et al., 1998, found no significant difference in efficacy between LAmB in lipid emulsion and AmB in dextrose.[92] The study by Hamill et al., 2010, observed superior safety outcomes with LAmB. Based on the evidence collected so far, clinicians should consider administering higher doses of LAmB (3 mg/kg/day) for quicker microbial conversion and shorter treatment duration in cryptococcal meningitis patients, as suggested by the study of Jadhav et al., 2010.[93] While the higher dosage of LAmB may result in increased costs, clinicians should weigh the clinical benefit against the financial burden, ensuring optimal treatment outcomes.

Given its comparable efficacy and better safety against adverse reactions, LAmB should be preferred over conventional formulations, especially in patients at risk of infusion-related reactions and nephrotoxicity, as highlighted by the study of Hamill et al., 2010.[75] Future studies should focus on long-term outcomes, including relapse rates and overall survival, to provide a deeper farsighted understanding into the efficacy and safety of LAmB in cryptococcal meningitis treatment.

However, there are a few limitations that must be taken into consideration while entirely relying upon the above-mentioned findings. The included studies have small sample sizes and may lack generalizability to broader populations. Some studies are retrospective or involve specific patient populations. Cost and availability of LAmB may vary across different healthcare settings in developing and developed countries.

Table 3. Studies showing efficacy of Liposomal Amphotericin B.

Author/ Year	Methodology	Main findings
Torre et al. /1998	Retrospective study on 30 AIDS patients with Cryptococcal meningitis comparing efficacy and safety of AmB in dextrose and in a lipid emulsion with a focus on clinical resolution and infusion-related adverse effects.[92]	AmB-IL showed similar efficacy to AmB dissolved in dextrose in treating Cryptococcal meningitis in AIDS patients. AmB-IL did not reduce infusion-related adverse effects such as nephrotoxicity and anemia. This study concludes that AmB-IL formulation is beneficial for treating Cryptococcal meningitis in AIDS patients, but it does not offer an advantage in reducing infusion-related adverse effects.
Jadhav et al. /2010	Prospective, randomized, multicenter study comparing 2 doses of LAmB (Higher dose of 3 mg/kg/day and lower dose of 1mg/kg/day) in adult patients with Cryptococcal meningitis and HIV/AIDS. Clinical efficacy, tolerability and mycological responses were assessed at different intervals.[93]	Higher dose of 3mg/day/kg of LAmB showed better efficacy, quicker microbial conversion of CSF and thereby, shortened treatment duration by 27% compared to lower dose of 1 mg/day/kg, despite the higher cost associated with the higher dose.
Hamill et al. /2010	Randomized, double blind clinical trial comparing efficacy and safety of different doses of LAmB and conventional AmB deoxycholate in patients with AIDS and acute Cryptococcal meningitis. Evaluations were performed at specific time points. Statistical analyses were conducted to compare outcomes among the treatment groups.[75]	LAmB at dosages of 3mg/kg/day is an equally efficacious alternative to AmB deoxycholate in patients with AIDS and Cryptococcal meningitis. LAmB had significantly lower infusion related reactions and nephrotoxicity compared to AmB.

Table 3. Continued.

Author /Year	Methodology	Main findings
Jarvis et al. /2022	Phase 3 randomized, controlled, noninferiority trial was conducted across five African countries to compare two treatments for HIV-positive adults with cryptococcal meningitis. Participants were randomly assigned in equal numbers to one of two groups: 1. Experimental Group: Received a single high dose of LAmB (10 mg per kilogram) on the first day, followed by 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day). 2. Control Group: Received the standard World Health Organization (WHO) treatment, consisting of amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by 7 days of fluconazole (1200 mg per day). The main objective was to measure the rate of death from any cause at 10 weeks. The goal of the study is to determine if a single high dose of LAmB, followed by 14 days of combination therapy, is as effective as the WHO-recommended treatment regimen.[94]	844 participants were randomized, 814 included in the intention-to-treat analysis. At the 10-week mark, 101 participants (24.8%; 95% confidence interval [CI], 20.7 to 29.3) in the LAmB group had died, compared to 117 participants (28.7%; 95% CI, 24.4 to 33.4) in the control group. Single-dose LAmB combined with flucytosine, and fluconazole was found to be noninferior to the WHO-recommended treatment for HIV-associated cryptococcal meningitis. Additionally, this regimen was associated with fewer adverse events.
Gupta et al. /2024	A 50-year-old man presented at a tertiary care hospital in North India with a short history of altered mental sensorium, and a history of low-grade fever and weight loss over several months. He tested positive for HIV-1. Cryptococcal antigen was detected in his CSF but not in his serum. While the CSF fungal culture was sterile, the fungal blood culture revealed the presence of C. neoformans. The patient was treated with a single high dose of LAmB, followed by a two-week course of fluconazole and flucytosine. After this initial treatment, he continued with daily fluconazole for consolidation and maintenance therapy. ART was initiated four weeks after the induction therapy. Six months later, the patient is doing well.[95]	Single-dose LAmB combined with fluconazole and flucytosine appears promising for treating disseminated cryptococcal infection in HIV-infected individuals.
Belinschi et al. /2024	A 47-year-old male with a medical history of heterosexually acquired HIV presented to the emergency department with complaints of a severe headache lasting for eight days. Subsequent blood cultures were positive for C. *neoformans*.[96]	In this case, the use of LAmB as the primary outpatient maintenance agent was necessitated by the patient's adverse reaction to fluconazole, highlighting the need for alternative treatment options. LAmB, with its once-weekly infusion schedule, provides benefits in terms of patient compliance and quality of life, despite being relatively more expensive than AmB.

Conclusion

The incidence of fungal meningitis, mainly cryptococcal meningitis, is drastically increased in patients suffering from HIV/AIDS. The reason for this is the decrease in immunity which makes the patient more susceptible. The mortality and morbidity rates are very high among these individuals if they do not receive proper treatment. In recent times several research have been carried out to find out the efficacy of various antifungal drugs. It has been reported that Liposomal Amphotericin B has proved to be very effective in most cases as compared to the other available fungal drugs. It also reduces the side effects including toxicity that occur with Amphotericin B Deoxycholate. However, it should be noted that no drug is 100% safe, and the dosage needs to be closely monitored to prevent any adverse reactions. In conclusion, the evidence supports the use of LAmB as an effective and safe treatment option for cryptococcal meningitis, particularly in immunocompromised patients, while minimizing adverse effects. However, further research and careful consideration of cost-effectiveness are needed to aid the clinical decision-making process and enhance patient outcomes.

Author Contributions

All authors made significant contributions to this research in the form of study design, acquisition of information, drafting, revising and critically reviewing the manuscript.

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References

1. Fisher, K. M., Montrief, T., Ramzy, M., et al, (2021). Cryptococcal meningitis: a review for emergency clinicians. *Internal & emergency medicine*, *16*, 1031-1042.
2. Tugume, L., Ssebambulidde, K., Kasibante, J., et al, (2023). Cryptococcal meningitis. *Nature Reviews Disease Primers*, *9*(1), 62.
3. Firacative, C., Meyer, W., & Castañeda, E. (2021). Cryptococcus neoformans and Cryptococcus gattii species complexes in Latin America: a map of molecular types, genotypic diversity, and antifungal susceptibility as reported by the Latin American Cryptococcal Study Group. *Journal of Fungi*, *7*(4), 282.
4. Hiesgen, J., Schutte, C., Olorunju, S., et al, (2017). Cryptococcal meningitis in a tertiary hospital in Pretoria, mortality and risk factors–A retrospective cohort study. *International journal of STD & AIDS*, *28*(5), 480-485.
5. Limper, A. H., Adenis, A., Le, T., et al, (2017). Fungal infections in HIV/AIDS. *The Lancet Infectious Diseases*, *17*(11), e334-e343.
6. Okurut, S., Boulware, D. R., Olobo, J., et al, (2020). Landmark clinical observations and immunopathogenesis pathways linked to HIV and Cryptococcus fatal central nervous system co-infection. *Mycoses*, *63*(8), 840-853.
7. Mesa-Arango, A. C., Scorzoni, L., & Zaragoza, O. (2012). It only takes one to do many jobs: Amphotericin B as antifungal and immunomodulatory drug. *Frontiers in microbiology*, *3*, 286.
8. Shafiei, M., Peyton, L., Hashemzadeh, M., et al, (2020). History of the development of antifungal azoles: A review on structures, SAR, and mechanism of action. *Bioorganic chemistry*, *104*, 104240.
9. Kauffman, C. A., Pappas, P. G., Sobel, J. D., et al, (2011). *Essentials of clinical mycology* (pp. 321-335). New York: Springer New York.
10. Buil, J. B., Hagen, F., Chowdhary, A., et al, (2018). Itraconazole, voriconazole, and posaconazole CLSI MIC distributions for wild-type and azole-resistant Aspergillus fumigatus isolates. *Journal of Fungi*, *4*(3), 103.
11. Demir, K. K., Butler-Laporte, G., Del Corpo, O., et al, (2021). Comparative effectiveness of amphotericin B, azoles and echinocandins in the treatment of candidemia and invasive candidiasis: A systematic review and network meta-analysis. *Mycoses*, *64*(9), 1098-1110.
12. Maertens, J. A. (2004). History of the development of azole derivatives. *Clinical Microbiology and Infection*, *10*, 1-10.

13. Sucher, A. J., Chahine, E. B., & Balcer, H. E. (2009). Echinocandins: the newest class of antifungals. *Annals of Pharmacotherapy*, *43*(10), 1647-1657.

14. Denning, D. W. (2002). Echinocandins: a new class of antifungal. *Journal of Antimicrobial Chemotherapy*, *49*(6), 889-891.

15. Schwarz, P., Dromer, F., Lortholary, O., et al, (2006). Efficacy of amphotericin B in combination with flucytosine against flucytosine-susceptible or flucytosine-resistant isolates of Cryptococcus neoformans during disseminated murine cryptococcosis. *Antimicrobial agents and chemotherapy*, *50*(1), 113-120.

16. Drew, R. H. (2019). Polyenes for prevention and treatment of invasive fungal infections. *Antifungal Therapy, Second Edition*, 155-175.

17. Sigera, L. S. M., & Denning, D. W. (2023). Flucytosine and its clinical usage. *Therapeutic advances in infectious disease*, *10*, 20499361231161387.

18. Vermes, A., Guchelaar, H. J., & Dankert, J. (2000). Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *Journal of Antimicrobial Chemotherapy*, *46*(2), 171-179.

19. Kauffman, C. A., Pappas, P. G., Sobel, J. D., et al, (2011). *Essentials of clinical mycology* (pp. 321-335). New York: Springer New York.

20. Singh, K. (2017). In Silico Studies on the Effect of Griseofulvin on Tubulin Protein of Cryptococcus neoformans and its In Vitro Validation. *The Journal of Microbiology, Biotechnology and Food Sciences*, *6*(6), 1280.

21. Petersen, A. B., Rønnest, M. H., Larsen, T. O., et al, (2014). The chemistry of griseofulvin. *Chemical reviews*, *114*(24), 12088-12107.

22. Aris, P., Wei, Y., Mohamadzadeh, M., et al, (2022). Griseofulvin: An updated overview of old and current knowledge. *Molecules*, *27*(20), 7034.

23. Verkhovskii, R. A., Kozlova, A. A., Lengert, E. V., et al, (2023). Cytotoxicity, Dermal Toxicity, and In Vivo Antifungal Effect of Griseofulvin-Loaded Vaterite Carriers Administered via Sonophoresis. *ACS Infectious Diseases*, *9*(5), 1137-1149.

24. Pagliano, P., Esposito, S., Ascione, T., et al, (2020). Burden of fungal meningitis. *Future Microbiology*, *15*(7), 469-472.

25. Stone, N. R., Bicanic, T., Salim, R., et al, (2016). Liposomal amphotericin B (AmBisome®): a review of the pharmacokinetics, pharmacodynamics, clinical experience and future directions. *Drugs*, *76*, 485-500.

26. Lestner, J. M., Howard, S. J., Goodwin, J., et al, (2010). Pharmacokinetics and pharmacodynamics of amphotericin B deoxycholate, liposomal amphotericin B, and amphotericin B lipid complex in an in vitro model of invasive pulmonary aspergillosis. *Antimicrobial agents and chemotherapy*, *54*(8), 3432-3441.

27. Takemoto, K., Yamamoto, Y., & Ueda, Y. (2006). Evaluation of antifungal pharmacodynamic characteristics of AmBisome against Candida albicans. *Microbiology and immunology*, *50*(8), 579-586.

28. Lewis, R. E., Liao, G., Hou, J., et al, (2007). Comparative analysis of amphotericin B lipid complex and liposomal amphotericin B kinetics of lung accumulation and fungal clearance in a murine model of acute invasive pulmonary aspergillosis. *Antimicrobial agents and chemotherapy*, *51*(4), 1253-1258.

29. Al-Nakeeb, Z., Petraitis, V., Goodwin, J., et al, (2015). Pharmacodynamics of amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B against Aspergillus fumigatus. *Antimicrobial agents and chemotherapy*, *59*(5), 2735-2745.

30. Shimizu, K., Osada, M., Takemoto, K., et al, (2010). Temperature-dependent transfer of amphotericin B from liposomal membrane of AmBisome to fungal cell membrane. *Journal of Controlled Release*, *141*(2), 208-215.

31. Papahadjopoulos, D., Jacobson, K., Nir, S., et al, (1973). Phase transitions in phospholipid vesicles Fluorescence polarization and permeability measurements concerning the effect of temperature and cholesterol. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *311*(3), 330-348.

32. Bekersky, I., Fielding, R. M., Dressler, D. E., et al, (2002). Plasma protein binding of amphotericin B and pharmacokinetics of bound versus unbound amphotericin B after administration of intravenous liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate. *Antimicrobial agents and chemotherapy*, *46*(3), 834-840.

33. Groll, A. H., Rijnders, B. J., Walsh, T. J., et al, (2019). Clinical pharmacokinetics, pharmacodynamics, safety and efficacy of liposomal amphotericin B. *Clinical Infectious Diseases*, *68*(Supplement_4), S260-S274.

34. Polak, A. (1979). Pharmacokinetics of amphotericin B and flucytosine. *Postgraduate Medical Journal*, *55*(647), 667-670.

35. Perfect, J. R., & Durack, D. T. (1982). Treatment of experimental cryptococcal meningitis with amphotericin B, 5-fluorocytosine, and ketoconazole. *Journal of Infectious Diseases*, *146*(3), 429-435.
36. Livermore, J., Howard, S. J., Sharp, A. D., et al, (2014). Efficacy of an abbreviated induction regimen of amphotericin B deoxycholate for cryptococcal meningoencephalitis: 3 days of therapy is equivalent to 14 days. *MBio*, *5*(1), 10-1128.
37. Andes, D., Safdar, N., Marchillo, K., et al, (2006). Pharmacokinetic-pharmacodynamic comparison of amphotericin B (AMB) and two lipid-associated AMB preparations, liposomal AMB and AMB lipid complex, in murine candidiasis models. *Antimicrobial agents and chemotherapy*, *50*(2), 674-684.
38. Lewis, R. E., Liao, G., Hou, J., et al, (2007). Comparative analysis of amphotericin B lipid complex and liposomal amphotericin B kinetics of lung accumulation and fungal clearance in a murine model of acute invasive pulmonary aspergillosis. *Antimicrobial agents and chemotherapy*, *51*(4), 1253-1258.
39. Adler-Moore, J. P., Proffitt, R. T., Olson, J. A., et al, (2017). Tissue pharmacokinetics and pharmacodynamics of AmBisome®(L-AmBis) in uninfected and infected animals and their effects on dosing regimens. *Journal of liposome research*, *27*(3), 195-209.
40. Takemoto, K., & Kanazawa, K. (2017). AmBisome: relationship between the pharmacokinetic characteristics acquired by liposomal formulation and safety/efficacy. *Journal of Liposome Research*, *27*(3), 186-194.
41. Dupont, B. (2002). Overview of the lipid formulations of amphotericin B. *Journal of Antimicrobial Chemotherapy*, *49*(suppl_1), 31-36.
42. Adler-Moore, J. P., & Proffitt, R. T. (2008). Amphotericin B lipid preparations: what are the differences? *Clinical Microbiology and Infection*, *14*, 25-36.
43. Kleinberg, M. (2006). What is the current and future status of conventional amphotericin B? *International journal of antimicrobial agents*, *27*, 12-16.
44. Hamill, R. J. (2013). Amphotericin B formulations: a comparative review of efficacy and toxicity. *Drugs*, *73*, 919-934.
45. Clemons, K. V., & Stevens, D. A. (2004). Comparative efficacies of four amphotericin B formulations—Fungizone, Amphotec (Amphocil), AmBisome, and Abelcet—against systemic murine aspergillosis. *Antimicrobial agents and chemotherapy*, *48*(3), 1047-1050.
46. Cifani, C., Costantino, S., Massi, M., et al, (2012). Commercially available lipid formulations of amphotericin B: are they bioequivalent and therapeutically equivalent. *Acta Biomed*, *83*(2), 154-63.
47. Perfect, J. R. (2017). The antifungal pipeline: a reality check. *Nature reviews Drug discovery*, *16*(9), 603-616.
48. Adler-Moore, J., & Proffitt, R. T. (2002). AmBisome: liposomal formulation, structure, mechanism of action and pre-clinical experience. *Journal of Antimicrobial Chemotherapy*, *49*(suppl_1), 21-30.
49. Ellis, M., Spence, D., de Pauw, B., et al, (1998). Amphotericin B: time for a new formulation? Journal of Antimicrobial Chemotherapy, 42(4), 597-609.
50. Cadena, J., Thompson, G. R., & Patterson, T. F. (2016). Invasive aspergillosis: current strategies for diagnosis and management. *Infectious Disease Clinics*, *30*(1), 125-142.
51. Hiemenz, J. W., & Walsh, T. J. (1996). Lipid formulations of amphotericin B: recent progress and future directions. *Clinical infectious diseases*, *22*(Supplement_2), S133-S144.
52. Wingard, J. R. (2002). Lipid formulations of amphotericins: are you a lumper or a splitter?. *Clinical infectious diseases*, *35*(7), 891-895.
53. Santangelo, R., Paderu, P., Delmas, G., et al, (2000). Efficacy of oral cochleate-amphotericin B in a mouse model of systemic candidiasis. *Antimicrobial agents and chemotherapy*, *44*(9), 2356-2360.
54. Mohr, J., Johnson, M., Cooper, T., et al, (2008). Current options in antifungal pharmacotherapy. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *28*(5), 614-645.
55. Johnson, M. D., Drew, R. H., & Perfect, J. R. (1998). Chest discomfort associated with liposomal amphotericin B: report of three cases and review of the literature. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *18*(5), 1053-1061.
56. Groll, A. H., Rijnders, B. J., Walsh, T. J., et al, (2019). Clinical pharmacokinetics, pharmacodynamics, safety and efficacy of liposomal amphotericin B. *Clinical Infectious Diseases*, *68*(Supplement_4), S260-S274.
57. Takazono, T., Hidaka, Y., Morimoto, S., et al, (2022). Comparison of liposomal amphotericin B

alone and in combination with flucytosine in the treatment of non-HIV Cryptococcal meningitis: A nationwide observational study. *Mycoses*, *65*(9), 897-902.

58. Ran, T. A. O., Jin-chuan, S. H. I., Yong-zheng, G. U. O., et al, (2019). Comparison of amphotericin B deoxycholate, amphotericin B liposome and voriconazole as induction treatment on HIV-related cryptococcal meningitis. *Electronic Journal of Emerging Infectious Diseases*, *4*(2), 97.
59. Rajasingham, R., Nalintya, E., Israelski, D. M., et al, (2022). Cost-effectiveness of single-dose AmBisome pre-emptive treatment for the prevention of cryptococcal meningitis in African low and middle-income countries. *Medical mycology*, *60*(2), myab078.
60. Groll, A. H., Giri, N., Petraitis, V., et al, (2000). Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental Candida albicans infection of the central nervous system. *The Journal of infectious diseases*, *182*(1), 274-282.
61. Andes, D., Safdar, N., Marchillo, K., et al, (2006). Pharmacokinetic-pharmacodynamic comparison of amphotericin B (AMB) and two lipid-associated AMB preparations, liposomal AMB and AMB lipid complex, in murine candidiasis models. *Antimicrobial agents and chemotherapy*, *50*(2), 674-684.
62. Gershkovich, P., Wasan, E. K., Lin, M., et al, (2009). Pharmacokinetics and biodistribution of amphotericin B in rats following oral administration in a novel lipid-based formulation. *Journal of antimicrobial chemotherapy*, *64*(1), 101-108.
63. Maertens, J. A., Madero, L., Reilly, A. F., et al, (2010). A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *The Pediatric infectious disease journal*, *29*(5), 415-420.
64. Caselli, D., Cesaro, S., Ziino, O., et al, (2012). A prospective, randomized study of empirical antifungal therapy for the treatment of chemotherapy-induced febrile neutropenia in children. *British journal of haematology*, *158*(2), 249-255.
65. Kubiak, D. W., Bryar, J. M., McDonnell, A. M., et al, (2010). Evaluation of caspofungin or micafungin as empiric antifungal therapy in adult patients with persistent febrile neutropenia: a retrospective, observational, sequential cohort analysis. *Clinical therapeutics*, *32*(4), 637-648.
66. Perfect, J. R. (2017). The antifungal pipeline: a reality check. *Nature reviews Drug discovery*, *16*(9), 603-616.
67. Wall, G., & Lopez-Ribot, J. L. (2020). Current antimycotics, new prospects, and future approaches to antifungal therapy. *Antibiotics*, *9*(8), 445.
68. Chang, Y. L., Yu, S. J., Heitman, J., et al, (2017). New facets of antifungal therapy. *Virulence*, *8*(2), 222-236.
69. Roemer, T., & Krysan, D. J. (2014). Antifungal drug development: challenges, unmet clinical needs, and new approaches. *Cold Spring Harbor perspectives in medicine*, *4*(5), a019703.
70. Fuentefria, A. M., Pippi, B., Dalla Lana, D. F., et al, (2018). Antifungals discovery: an insight into new strategies to combat antifungal resistance. *Letters in applied microbiology*, *66*(1), 2-13.
71. Rex, J. H., Walsh, T. J., Sobel, J. D., et al, (2000). Practice guidelines for the treatment of candidiasis. *Clinical infectious diseases*, *30*(4), 662-678.
72. Pappas, P. G., Kauffman, C. A., Andes, D. R., et al, (2016). Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clinical infectious diseases*, *62*(4), e1-e50.
73. Colombo, A. L., Guimarães, T., Camargo, L. F. A., et al, (2013). Brazilian guidelines for the management of candidiasis–a joint meeting report of three medical societies: Sociedade Brasileira de Infectologia, Sociedade Paulista de Infectologia and Sociedade Brasileira de Medicina Tropical. *The Brazilian Journal of Infectious Diseases*, *17*(3), 283-312.
74. Kullberg, B. J., Verweij, P. E., Akova, M., et al, (2011). European expert opinion on the management of invasive candidiasis in adults. *Clinical Microbiology and Infection*, *17*, 1-12.
75. Hamill, R. J., Sobel, J. D., El-Sadr, W., et al, (2010). Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clinical infectious diseases*, *51*(2), 225-232.
76. Aguirre, J. P. B., & Hamid, A. M. R. (2015). Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. *Cochrane Database of Systematic Reviews*, (11).
77. Jadhav, M., Jadhav, P., Shinde, V., et al, (2013). Liposomal Amphotericin B for the Treatment of Cryptococcal Meningitis in HIV/AIDS Patients in

India A Pilot Pharmacokinetic Study. *Clinical Pharmacology in Drug Development*, *2*(1), 48-52.

78. Safdar, A., Ma, J., Saliba, F., et al. (2010). Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. *Medicine*, *89*(4), 236-244.
79. Barrett, J. P., Vardulaki, K. A., Conlon, C., et al, (2003). A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. *Clinical therapeutics*, *25*(5), 1295-1320.
80. Rajasingham, R., Smith, R. M., Park, B. J., et al, (2017). Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet infectious diseases*, *17*(8), 873-881.
81. Advice, W. R. (2011). Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. *Geneva: WHO*.
82. Chen, T., Mwenge, L., Lakhi, S., et al, (2019). Healthcare costs and life-years gained from treatments within the advancing cryptococcal meningitis treatment for Africa (ACTA) trial on cryptococcal meningitis: A comparison of antifungal induction strategies in sub-Saharan Africa. *Clinical Infectious Diseases*, *69*(4), 588-595.
83. Jackson, A. T., Nussbaum, J. C., Phulusa, J., et al, (2012). A phase II randomized controlled trial adding oral flucytosine to high-dose fluconazole, with short-course amphotericin B, for cryptococcal meningitis. *Aids*, *26*(11), 1363-1370.
84. Alvarez-Uria, G., Midde, M., Battula, J., et al, (2018). Safety and tolerability of intrathecal liposomal amphotericin B (AmBisome) for cryptococcal meningitis: a retrospective study in HIV-infected patients. *Therapeutic Advances in Infectious Disease*, *5*(5), 77-81.
85. Yuchong, C., Jianghan, C., Hai, W., et al, (2011). Lumbar puncture drainage with intrathecal injection of amphotericin B for control of cryptococcal meningitis. *Mycoses*, *54*(4), e248-e251.
86. Alvarez-Uria, G., Midde, M., Pakam, R., et al, (2015). Short-Course Induction Treatment with Intrathecal Amphotericin B Lipid Emulsion for HIV Infected Patients with Cryptococcal Meningitis. *Journal of Tropical Medicine*, *2015*(1), 864271.
87. Ho, J., Fowler, P., Heidari, A., et al, (2017). Intrathecal amphotericin B: a 60-year experience in treating coccidioidal meningitis. *Clinical Infectious Diseases*, *64*(4), 519-524.
88. Galgiani, J. N., Ampel, N. M., Blair, J. E., et al, (2005). Coccidioidomycosis. *Clinical Infectious Diseases*, *41*(9), 1217-1223.
89. Clemons, K. V., Sobel, R. A., Williams, P. L., et al, (2001). Comparative toxicities and pharmacokinetics of intrathecal lipid (amphotericin B colloidal dispersion) and conventional deoxycholate formulations of amphotericin B in rabbits. *Antimicrobial agents and chemotherapy*, *45*(2), 612-615.
90. Mete, B., Saltoglu, N., Vanli, E., et al, (2016). Simultaneous cryptococcal and tuberculous meningitis in a patient with systemic lupus erythematosus. *Journal of Microbiology, Immunology and Infection*, *49*(2), 289-294.
91. Capilla, J., Flavia, A., Mayayo, E., et al, (2013). Efficacy of intrathecal liposomal amphotericin B plus oral posaconazole in the treatment of acute meningeal cryptococcosis in a murine model.
92. Torre, D., Casari, S., Speranza, F., et al, (1998). Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrobial agents and chemotherapy*, *42*(6), 1346-1349.
93. Jadhav, M. P., Bamba, A., Shinde, V. M., et al, (2010). Liposomal amphotericin B (FungisomeTM) for the treatment of cryptococcal meningitis in HIV/AIDS patients in India: a multicentric, randomized controlled trial. *Journal of postgraduate medicine*, *56*(2), 71-75.
94. Jarvis, J. N., Lawrence, D. S., Meya, D. B., et al, (2022). Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *New England Journal of Medicine*, *386*(12), 1109-1120.
95. Gupta, C., Dogra, P., Jain, V., et al, (2024). HIV-associated disseminated Cryptococcosis-An Unusual clinical and diagnostic picture with successful cure by single dose Liposomal Amphotericin B treatment. *Diagnostic Microbiology and Infectious Disease*, 116217.
96. Belinschi, V., Iheagwara, C., & Muhanna, A. (2024). Once-Weekly Liposomal Amphotericin B Use for Maintenance and Consolidation Phase Treatment of Cryptococcal Meningitis in Patients With AIDS. *Cureus*, *16*(3).