Amphotericin-B in Dermatology

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Introduction

The molecule Amphotericin B (AmB) has stood the test of time in being one of the most potent and reliable antifungal drugs against invasive fungal infections. As the human race continues to cope with the ongoing COVID19 pandemic, a new enemy in the form of mucormycosis has emerged prompting us to once again turn towards this age-old drug to be the savior.[1] This review reappraises the drug profile of AmB with special emphasis on its use in the field of dermatology.

Pharmacology

AmB, a macrolide polyene antifungal, is obtained from soil actinomycete *Streptomyces nodosus* via the process of fermentation. Because AmB is amphoteric and water-insoluble, only parenteral formulations are available. AmB deoxycholate (d-AmB) was the first preparation marketed in 1959. As a result of infusion-related reactions and nephrotoxicity, lipid-based formulations were prepared such as liposomal AmB (l-AmB), AmB lipid complex (ABLC), and AmB colloidal dispersion (ABCD). Recently, various topical formulations of AmB have been made and successfully used in patients of cutaneous leishmaniasis and mucormycosis. The salient points related to pharmacokinetics, dosage, and toxicities of the four formulations of AmB have been summarized in Table 1.[2,3]

Mechanism of Action

AmB acts via selective binding to ergosterol, a key component of the fungal cell membrane, via both the hydrophobic (polyene hydrocarbon) and hydrophilic region (polyhydroxyl chain). Eight AMB molecules attach to eight ergosterol molecules via the polyene hydrophobic chain, leading to the formation of pores on the cell membrane. Pore formation results in K^+ efflux, fungal glycolysis inhibition, and Mg^{++} efflux with simultaneous proton influx. The increased acidification of fungal cytoplasm results in the precipitation of proteins and subsequent cell death. Additional mechanisms proposed include oxidative damage via free radical formation and stimulation of the phagocytic system to aid fungal clearance [Figure 1].[2]

FDA Approved Indications of Liposomal AmB[3]

1. Empirical therapy for presumed fungal infection in febrile, neutropenic patients.
2. Cryptococcal meningitis in HIV infected patients
3. Patients with *Aspergillus* species, *Cryptococcus* species, or *Candida* species infection refractory to amphotericin B deoxycholate, or patients with renal impairment or prior hypersensitivity to amphotericin B deoxycholate.
4. Treatment of visceral leishmaniasis.

Dermatological Uses of AmB

a. Leishmaniasis

The action of AmB in leishmaniasis is attributed to its selective affinity to bind to ergosterol present in the parasite's cell membrane. Subsequent sequestration of host cell membrane cholesterol by AmB prevents the macrophage-parasite linkage. Other mechanisms postulated include cell membrane disruption by lipid peroxidation, endosome-lysosome fusion inhibition, apoptosis, and stimulation of INF-Y production resulting in macrophage activation.[4]

- Mucocutaneous leishmaniasis:
  - i. Systemic therapy

    AmB and miltefosine are the preferred drug of choice. L-AmB is

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Figure 1: Mechanism of action of Amphotericin B

Table 1: Pharmacokinetics, dosage and toxicities of parenteral formulations of AmB

	D-AmB[2]	L-AmB[3]	ABLC	ABCD
FDA approval	1959	1997	1995	1996
Recommended dose	1 mg/kg	3 mg/kg	5 mg/kg	3-4 mg/kg
Composition	50 mg AMB with 41 mg of sodium deoxycholate	Hydrogenated soyphosphatidylcholine: cholesterol; distearoyl phosphotidyl-glycerol: AMB in ratio of 2:1:0.8:1	L-alpha-dimyristoyl phosphotidylcholine and L-alpha-dimyristoyl phosphotidyl glycerol in 7:3.	Cholesteryl sulphate and AMB 1:1
Structural arrangement	-	Unilamellar vesicle	Ribbons	Discs
Pharmacokinetics	Upon infusion, dissociates from deoxycholate and attaches to plasma lipoproteins LDL and HDL (mainly LDL form) via lipid transfer protein (LTP). Acheives Cmax of 1.5-2 mg/L with Vd: 2.4-4 L/kg Demonstrates Triphasic plasma profile with an elimination half-life of 15 days.	Small size and negative charge allow substantial escape from the mononuclear phagocytic system, resulting in higher Cmax and higher AUC. Triphasic plasma profile with a long terminal half-life of 152 h	The large molecule, engulfed rapidly by macrophages and sequestered in a mononuclear phagocytic system resulting in lower Cmax, high Vd, and low AUC.	Upon infusion, ABCD complex does not dissociate and is rapidly engulfed by the macrophage phagocytic system. Lower Cmax results
Excretion	30% renal and 42.5% in feces as unchanged drug	<10% excreted in urine and feces after 1 week	-	-
Tissues	Highest in spleen and liver	Highest in liver and spleen	Highest in Liver spleen and lungs	-
Toxicity	Acute infusion-related side effects and dose-related nephrotoxity is seen	Infusion-related and nephrotoxicity are minimal up to 7.5-15 mg/kg doses	Infusion-related toxicities and nephrotoxicity are less	Infusion-related toxicities more in patients receiving >4 mg/kg doses

the standard formulation preferred. Recommended WHO dosing is 2–3 mg/kg per day, by infusion, up to 40–60 mg/kg total dose.[5] Immunocompromised patients often need higher and prolonged therapy. The treatment regime comprises 3 mg/kg L-AMB for 5 consecutive days followed by the 6th dose on day 10.[6] In a review of Old World cutaneous and mucosal leishmaniasis among immunocompetent individuals, 85% (17/20) and 54% (7/13) cases were cured with L-AmB, respectively.[7] Similarly, in patients of new world mucosal leishmaniasis, 93.1% (27/29) cure was observed with a total cumulative dose being 32.5 mg/kg. Soloman *et al*.[8] have reported successful results in a series of seven patients with new world cutaneous leishmaniasis

ii. Topical therapy:

The first successful use described was in 1999 by Vardy *et al*.[9] using AmB in 5% ethanol. The aim to develop a topical formulation was to prevent systemic toxicity associated with injectable AmB. A randomized controlled trial comparing intralesional Glucantime injection (48.3% efficacy) with topical liposomal AmB formulation (44% efficacy) showed no statistically significant difference in efficacy among patients having old world cutaneous leishmaniasis.[10] Similarly, Lopez *et al*.[11] studied oil in water emulsion containing 3% AmB in patients with new world cutaneous leishmaniasis. Complete resolution was observed in 39.4% and 35.3% of patients on twice daily and thrice daily application, respectively. As of now, studies regarding topical AmB are not encouraging for cutaneous leishmaniasis. However, various other formulations of topical AmB such as liposomal, nanoparticles, ultra-deformable liposomes, and micro needling–based delivery are under trials for potential application in localized cutaneous leishmaniasis.[4]

iii. Intralesional therapy:
The first use of intralesional AmB was by Vahid *et al*.[12] where 2 mg/mL was injected into lesions weekly for up to 12 weeks with 61.4% of the patients showing complete recovery. A comparative trial has shown AmB 2.5 mg/mL to be equally efficacious as 5 mg/mL.[13]

- Post kala azar dermal leishmaniasis:
L-AmB is the second-line treatment of post kala azar dermal leishmaniasis in patients where miltefosine is contraindicated.[14] In a comparative trial comparing two different doses of AMB, low dose AMB (0.5 mg/kg) showed a better side effect without compromising efficacy.[15] Combination therapy of L-AmB and miltefosine has been shown to be superior in efficacy and safety in patients with PKDL.[16]
Recommended dosing:
  i. Africa: L-AmB: 2.5 mg/kg per day by infusion for 20 days
  ii. Asian countries:
  D-AmB: 1 mg/kg per day by infusion, up to 60–80 doses over 4 months.[5]
  L-AmB: 30 mg/kg in 6 weekly divided doses of 5 mg/kg

b. Cutaneous mucormycosis

- Systemic therapy:
It is caused by opportunistic fungi of class Glomerulomycota via penetrative trauma, commonly affecting patients with immunosuppression and uncontrolled diabetes. Treatment of choice is AMB along with surgical debridement and control of underlying immunosuppression. L-AmB is preferred to d-AmB because of its better safety profile. Treatment is to be started within 5 days of diagnosis. Recommended duration is up to clinical or radiological resolution or at least 6–8 weeks of therapy. Disseminated disease, delay in the initiation of treatment, and underlying immunosuppression are poor prognostic factors.[17]
Recommended dosing:
  i. D-AMB: 0.5–1 mg/kg/day in immunocompetent and 1–1.5 mg/kg/day in immunosuppressed individuals.
  ii. L-AmB: 5–10 mg/kg/day.
  Successful use of L-AmB in cutaneous mucormycosis in preterm neonates and infants has also been described.[18]
- Topical therapy:
A case of severe necrotizing skin and soft tissue mucormycosis successfully treated with systemic and topical AmB in an infant with lineage leukemia has been described. Another patient with vaginal mucormycosis treated with topical AmB has also been reported in the literature.[19,20]

c. Congenital candidiasis and neonatal candidiasis:

- Systemic therapy:
Systemic therapy with AMB is recommended in neonates with widespread dermatitis due to *Candida*, disseminated invasive disease, respiratory distress in the immediate neonatal period and/or sepsis. AmB at the dosage of 0.5–1 mg/kg/day is preferred, whereas L-AmB (35 mg/kg/day) is reserved for invasive cases or patients with renal insufficiency.[21] Systemic therapy is continued for a duration of 21–28 days.[22]
- Topical therapy:
  - Topical formulation of AmB has been used for the treatment of oral candidiasis, but the availability of such formulations is a major limiting factor.
  - The infectious disease society of America recommends the use of amphotericin B deoxycholate oral suspension as an alternative for fluconazole-refractory oral candidiasis.[23]
- Cases of resistant candidiasis caused by *Candida glabrata* and *Candida krusei* successfully treated with topical AmB have been described.[24,25]

d. Other indications:

- Anecdotal case reports of encouraging results with AmB have been described in cutaneous fusariosis,[26] protothecosis,[27] primary cutaneous aspergilloisis,[28] cutaneous histoplasmosis,[29] chromoblastomycosis (oral[30] and intralesional[31]), and blastomycosis.[32]
- Successful treatment of nondermatophytic molds such as fusarium and other species which do not respond to standard onychomycosis treatment has shown success in a small series of eight patients with topical AmB.[33]

Contraindications

AmB is contraindicated in those patients with known hypersensitivity to it or one of the preservatives.[34]

Storage and Administration

To be stored in dry form at 2–8°C away from light. The salient points to remember during infusion and monitoring of AmB have been summarized in Table 2.

D-AmB: A total of 50 mg vial is reconstituted with 10 mL sterile water (5 mg/mL) and shaken till the solution becomes clear. This is further diluted to 0.1 mg/mL with 500 mL 5% dextrose and then administered immediately.[34]

L-AmB: A total of 50 mg is reconstituted with 12 mL sterile water (4 mg/mL) and shaken to obtain clear fluid. Further dilution with an appropriate amount of reconstituted solution and 5% dextrose can be done to provide 1–2 mg/mL concentration for adults and 0.2–0.5 mg/mL concentration for infants and small children.[35]

Table 2: Salient points during infusion and monitoring of AmB:

Intravenous infusion of AmB	Test dose: A test dose of 0.1 mg/kg, and total not exceeding 1 mg is given by infusion over 20-60 min.
	Infusion after test dose is given over 2-6 h usually via a distal vein.
	Pre-treatment with acetaminophen, diphenhydramine, or corticosteroids administered approximately 30 min before infusion can be done in patients developing infusion-related toxicities.
	Proper hydration and potassium supplementation are important.
	Treatment should always be given in hospitals to allow continuous monitoring of patients.
Monitoring during AmB therapy	Infusion-related toxicities :
	Very common during d-AmB therapy such as nausea, vomiting, and chills. They tend to occur either immediately or within 15 min-3 h of infusion.
	Nephrotoxicity :
	Common with d-AmB
	Daily monitoring of serum creatinine is recommended. Consider switching to liposomal AmB in case serum creatinine rises over 2.5 mg/dL or reduction of the dose of d-AmB by 50%.
	Electrolytes:
	Hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia are noted with AmB therapy. Any signs of hypokalemia, such as muscle weakness, cramps, and drowsiness should prompt immediate ECG and management of serum potassium levels. The need for potassium and magnesium supplementation along with hydration with normal saline during amphotericin B infusions should be monitored.

Adverse Effects

The adverse effect profile of AmB has been summarized in Table 3.

Drug Interactions

As AMB is not metabolized by the cytochrome p450 pathway, the documented drug-drug interactions are limited. Dose-dependant nephrotoxicity and infusion-related electrolyte imbalance can be augmented by ongoing concomitant medication. Tacrolimus or cyclosporine used in kidney transplant patients increases AMB-related toxicity. Increased risk of hypokalemia occurs with the concomitant use of digoxin and corticosteroids. corticosteroids.[42]

AmB in Paediatric Population

The safety and effectiveness of AmB in pediatric leishmaniasis have been well documented in the literature. D-AmB is more hepatotoxic than L-AmB with no difference in infusion-related toxicities or nephrotoxicity. The adverse effect profile is probably better because of higher drug clearance and a smaller volume of distribution.[43] In a retrospective study of 70 pediatric patients with cutaneous leishmaniasis, 83% cure rates have been observed with a good safety profile.[44] Recommended dosing is similar to adults. (3–5 mg/kg/day for 5 days and then another dose on day 10).

AmB in Pregnancy and Lactation

Pregnancy: AmB is a category B drug and thus can be used if clinically indicated. It is the safest antifungal drug during pregnancy with established safety and efficacy of both liposomal and d-AmB.[45]

Lactation: Whether AmB gets secreted in breast milk is not known, but because it is highly protein-bound, has a large molecular weight, and is not absorbed orally, it can be used in nursing mothers but with caution.[46]

AmB in Special Population

Patients with renal impairment: No dose adjustment is necessary for patients with renal impairment based on CrCl estimate. Liposomal AmB has been successfully administered in patients with pre-existing renal impairment.[47,48]

Patients with hepatic impairment: Effect of liposomal AmB in patients with hepatic impairment is not known[48]

AmB Resistance

Fortunately, resistance to AmB is still rare compared to other anti-fungal drugs. Two possible theories have been put forward for the same. One is that AmB targets a major cell membrane component, ergosterol unlike other antifungals which target an enzyme. Another theory proposed is an association of AmB with severe fitness trade-offs.[49,50] Resistance that is MIC>2 mg/L is mostly species-specific and has emerged slowly with some clinical isolates with AmB. Studies on drug combination *in vitro* and *in vivo* have suggested that imidazoles can induce AmB resistance. The following methods of AmB resistance have been suggested:

1. Alterations in sterol composition in the fungal cell membrane. It involves mutations in genes related biosynthesis pathway. Mutations in *Candida albicans* (ERG 3, 11 mutation; ERG11 and loss

Table 3: Adverse effect profile of AmB

	Acute infusion-related side effects	Dose dependent Nephrotoxicity	Cutaneous side effects	Rare side effects:
Features	Presents within 2–6 h of infusion with features of fever, chills, rigors, nausea, vomiting, arthralgias, and headaches. Transient sub sternal chest discomfort, respiratory distress, and flank pain have also been described which resolves by discontinuation and intravenous diphenhydramine. Predominantly observed with d-D-AmB and ABCD and rarely with L-AmB and AMLC	Observed at doses of 0.7-1 mg/kg of d-AmB. These side effects are rarely observed with l-AmB. The abundance of LDL receptor on renal tubular cells and relative lack of HDL receptor results in the majority of uptake by renal tubules in the case of d-AmB. L-AmB on the other hand due to its small size and negative charge has reduced LTP mediated transfer to lipoprotein LDL resulting in higher HDL form results and subsequent decreased renal tubular uptake.	Urticarial reactions as part of infusion-related toxicities and thrombophlebitis at the injection site occur commonly with AMB. Rotation of intravenous catheters, use of intravenous saline after each dose of AMB, longer duration of infusion and proper nursing care can help to reduce incidence.[37] A case of leucocytoclastic vasculitis and Drug rash with eosinophilia and systemic symptoms (DRESS) has been described with L-AmB.[38,39]	New-onset dilated cardiomyopathy with associated heart failure has been reported. In these patients, symptoms subside within 6 months of discontinuation.[41] Acute elevation of bilirubin, transaminases, pancreatitis, and pseudo-hypophosphatemia have also been observed with L-AMB.[40]
Pathogenesis	Release of pro-inflammatory cytokine expressions such as IL-1B, TNF-alpha, IL-6, and IL-8 After recognition via toll-like receptor and trans membrane signaling protein CD14.[2]	Vasoconstriction of afferent renal arterioles results in decreased renal blood flow and glomerular filtration rate leading to nephrotoxicity.[36]	Urticarial reactions occur due to liposomal activation of the complement cascade and subsequent release of anaphylatoxins (C3a and C5a).[40]	-

of function ERG5), *Candida neoformans* (ERG2 mutation), and *Candida haemolonii* (ERG11, ERG3, ERG2, and ERG6 mutation) have been reported.[49,51]

2. Reduction in polyene-induced oxidative stress may allow better tolerability to AmB. Intrinsically, AmB resistant organisms such as *Aspergillus tereus* have shown this mechanism of resistance.[52]
3. Alteration in the fungal cell wall has also shown AmB resistance. An increase in the 1, 3 α-glucan fraction and 1,3-β-glucan in *Aspergillus flavus* and *Candida tropicalis,* respectively have been postulated to cause resistance.[53,54]

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Conflicts of interest

There are no conflicts of interest.

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