Amphotericin-B in Dermatology

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 Mg²⁺ 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

How to cite this article: Agarwal A, Kar BR. Amphotericin-B in dermatology. Indian Dermatol Online J 2022;13:152-8.
Received: 10-Sep-2021. Revised: 06-Nov-2021. Accepted: 07-Nov-2021. Published: 24-Jan-2022.

Address for correspondence:
Dr. Akash Agarwal, Senior Resident, Department of Dermatology, IMS and SUM Hospital, Bhubaneswar - 751 003, Odisha, India. E-mail: akash.22.1995@gmail.com
the standard formulation preferred. Recommended WHO dosing is 2–3 mg/kg per day, by infusion, up to 40–60 mg/kg total dose.\textsuperscript{[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 6\textsuperscript{th} dose on day 10.\textsuperscript{[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.\textsuperscript{[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 \textit{et al.}\textsuperscript{[8]} have reported successful results in a series of seven patients with new world cutaneous leishmaniasis.

\textbf{ii. Topical therapy:} The first successful use described was in 1999 by Vardy \textit{et al.}\textsuperscript{[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 intraleosomal 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.\textsuperscript{[10]} Similarly, Lopez \textit{et al.}\textsuperscript{[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.\textsuperscript{[4]}

---

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

|                | D-AmB\textsuperscript{[2]} | L-AmB\textsuperscript{[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 soyphatidylcholine: cholesterol; diesteroyl 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), Achieves Cmax of 1.5-2 mg/L with Vd: 2.4-4 L/kg | Small size and negative charge allow substantial escape from the mononuclear phagocytic system, resulting in higher Cmax and higher AUC. Demonstrates 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 nephrotoxicity 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 |
iii. Intraläsional therapy:
The first use of intraläsional 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.[9]
  - 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 aspergillosis,[28] cutaneous histoplasmosis,[29] chromoblastomycosis (oral[30] and intraläsional[31]), and blastomycesis.[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.[33]
Amphotericin B

**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. In a retrospective study of 70 pediatric patients with cutaneous leishmaniasis, 83% cure rates have been observed with a good safety profile. 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.

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.

**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.

Patients with hepatic impairment: Effect of liposomal AmB in patients with hepatic impairment is not known.

**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. 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
of function ERG5), Candida neoformans (ERG2 mutation), and Candida haemoloni (ERG11, ERG3, ERG2, and ERG6 mutation) have been reported. 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. 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ravani SA, Agrawal GA, Leuva PA, Modi PH, Amin KD. Rise of the phoenix: Mucomycosis in COVID-19 times. Indian J Ophthalmol 2021;69:1563-8.
2. Hamill RJ. Amphotericin B formulations: A comparative review of efficacy and toxicity. Drugs 2013;73:919-34.
3. Steimbach LM, Tonin FS, Virtuoso S, Borba HH, Sanches AC, Wiens A, et al. Efficacy and safety of amphotericin B lipid-based formulations-A systematic review and meta-analysis. Mycoses 2017;60:146-54.
4. Lanza JS, Pomel S, Loiseau PM, Frézard F. Recent advances in amphotericin B delivery strategies for the treatment of leishmaniases. Expert Opin Drug Deliv 2019;16:1063-79.
5. World Health Organization Control of the Leishmaniases 2010. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf. [Last accessed on 2021 Jun 04].
6. Solomon M, Pavlotsky F, Leshem E, Ephros M, Trau H, Schwartz E. Liposomal amphotericin B treatment of cutaneous leishmaniasis due to Leishmania tropica. J Eur Acad Dermatol Venereol 2011;25:973-7.
7. Mosimann V, Neumayr A, Paris DH, Blum J. Liposomal amphotericin B treatment of Old World cutaneous and mucosal leishmaniasis: A literature review. Acta Trop 2018;182:246-50.
8. Solomon M, Baum S, Barzilai A, Scope A, Trau H, Schwartz E. Liposomal amphotericin B in comparison to sodium stibogluconate for cutaneous infection due to Leishmania braziliensis. J Am Acad Dermatol 2007;56:126-9.
9. Vardy D, Barenholz Y, Cohen R, Zvulunov A, Biton A, Klaus S, et al. Topical amphotericin B for cutaneous leishmaniasis. Arch Dermatol 1999;135:856-7.
10. Layegh P, Rajabi O, Jafari MR, Emmangholi Tabar Malekshah P, Moghimian T, Ashraf H, et al. Efficacy of topical liposomal amphotericin B versus intralesional meglumine antimoniate (glucantime) in the treatment of cutaneous leishmaniasis. J Parasitol Res 2011;2011:656523. doi: 10.1155/2011/656523.
11. López L, Vélez I, Asela C, Cruz C, Alves F, Robledo S, et al. A phase II study to evaluate the safety and efficacy of topical 3% amphotericin B cream (Amofolesh) for the treatment of uncomplicated cutaneous leishmaniasis in Colombia. PLoS Negl Trop Dis 2018;12:e006653.
12. Vahid MG, Elham V, Bita K, Yalda N. Efficacy of intralesional amphotericin B in cutaneous leishmaniasis. Indian J Dermatol 2014;59:631.
13. Goswami P, Ghiya BC, Kumar V, Rekha S, Mehta RD. Comparison of efficacy of two different concentrations of intralasional amphotericin B in the treatment of cutaneous leishmaniasis; A randomized controlled trial. Indian Dermatol Online J 2019;10:627-31.

14. Pandey K, Pal B, Siddiqui NA, Lal CS, Ali V, Bimal S, et al. A randomized, open-label study to evaluate the efficacy and safety of liposomal amphotericin B (AmBisome) versus miltefosine in patients with post-kala-azar dermal leishmaniasis. Indian J Dermatol Venereol Leprol 2021;87:34-41.

15. Rabi Das VN, Siddiqui NA, Pal B, Lal CS, Verma N, Kumar A, et al. To evaluate efficacy and safety of amphotericin B in two different doses in the treatment of post kala-azar dermal leishmaniasis (PKDL). PLoS One 2017;12:e0174497.

16. Ramesh V, Dixit KK, Sharma N, Singh R, Salotra P. Assessing the Efficacy and Safety of liposomal amphotericin B and miltefosine in combination for treatment of post Kala-Azar dermal leishmaniasis. J Infect Dis 2020;221:608-17.

17. Castrejón-Pérez AD, Welsh EC, Miranda I, Ocampo-Candiani J, Welsh O. Cutaneous mucormycosis. An Bras Dermatol 2017;92:304-11.

18. Lowe CD, Sainat RJ, Stagliano DR, Morgan MM, Green BP. Primary cutaneous mucormycosis in an extremely preterm infant successfully treated with liposomal amphotericin B. Pediatr Dermatol 2017;34:e116-9.

19. Di Pentima MC, Chan S, Powell J, Napoli JA, Walter AW, Walsh TJ. Topical amphotericin B in combination with standard therapy for severe necrotizing skin and soft-tissue mucormycosis in an infant with bilateral leukemia: Case report and review. J Pediatr Hematol Oncol 2014;36:e468-70.

20. Sobel JD. Vaginal mucormycosis: A case report. Infect Dis Obstet Gynecol 2001;9:117-8.

21. Jagtap SA, Saple PP, Dhaliat SB. Congenital cutaneous candidiasis: A rare and unpredictable disease. Indian J Dermatol 2011;56:92-3.

22. Aruna C, Seetharam K. Congenital candidiasis. Indian Dermatol Online J 2014;5, Suppl S1:44-7.

23. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 Update by the infectious diseases society of America. Clin Infect Dis 2016;62:e1-50.

24. Chamorro-de-Vega E, Gil-Navarro MV, Perez-Blanco JL. Treatment of refractory Candida kruzi vaginitis with topical amphotericin B. Tratamiento de la vaginitis refractaria por Candida kruzi con anfotericina B tópica. Med Clin (Bac) 2016;147:565-6.

25. Shann S, Wilson J. Treatment of Candida glabrata using topical amphotericin B and flucytosine. Sex Transm Infect 2003;79:265-6.

26. Neuberger S, Massenkil G, Seibold M, Lutz C, Tamm I, le Coutre P, et al. Successful salvage treatment of disseminated cutaneous fusariosis with liposomal amphotericin B and terbinafine after allogeneic stem cell transplantation. Transpl Infect Dis 2008;10:290-3.

27. Mayorga J, Barba-Gómez JF, Verduzzo-Martinez AP, et al. Proteothecosis. Clin Dermatol 2012;30:432-6.

28. Gallais F, Denis J, Koobar O, Dillenseger L, Astruc D, Herbrecht R, et al. Simultaneous primary invasive cutaneous aspergillosis in two preterm twins: Case report and review of the literature. BMC Infect Dis 2017;17:535.

29. Sinha S, Agrawal D, Sardana K, Malhotra P. Cutaneous histoplasmosis: An unusual presentation with nasal obstruction. Indian Dermatol Online J 2020;11:612-5.

30. Park SG, Oh SH, Suh SB, Lee KH, Chung KY. A case of chromoblastomycosis with an unusual clinical manifestation caused by Phialophora verrucosa on an unexposed area: Treatment with a combination of amphotericin B and 5-flucytosine. Br J Dermatol 2005;152:560-4.

31. Ranawaka RR. Treatment of chromoblastomycosis with a combination of debulking surgery, intralasional amphotericin B, and oral terbinafine [published online ahead of print, 2021 Apr 7]. Int J Dermatol 2021;60:1040-1.

32. Ortega-Loayza AG, Nguyen T. Cutaneous blastomycosis: A clue to a systemic disease. An Bras Dermatol 2013;88:287-9.

33. Sinha S, Sardana K. Antifungal efficacy of amphotericin b against dermatophytes and its relevance in recalcitrant dermatophytoses: A commentary. Indian Dermatol Online J 2018;9:120-2.

34. Amphotericin B (conventional) (amphotericin B deoxycholate) dosing, indications, interactions, adverse effects, and more. 2019. Available from: https://reference.medscape.com/drug/amphotericin-b-conventional-amphotericin-b-deoxycholate-342582#11. [Last accessed on 2021 Jun 07].

35. AmBisome (amphotericin B liposomal) dosing, indications, interactions, adverse effects, and more. 2020. Available from: https://reference.medscape.com/drug/amphotericin-b-liposomal-999576#11 [Last accessed on 2021 Jun 07].

36. Sawaya BR, Briggs JP, Schnerrmann J. Amphotericin B nephrotoxicity: The adverse consequences of altered membrane properties. J Am Soc Nephrol 1995;6:154-64.

37. Ahimbisibwe C, Kizwera R, Ndyetukira JF, Kugonza F, Sadiq A, Hullsiek KH, et al. Management of amphotericin-induced phlebitis among HIV patients with cryptococcal meningitis in a resource-limited setting: A prospective cohort study. BMC Infect Dis 2019;19:558.

38. Cagatay AA, Taranoglu O, Alpay N, Tufan F, Karadeniz E, Kapnaz M, et al. Amphotericin B-induced cutaneous leucoyctoclastic vasculitis: Case report. Mycoses 2008;51:81-2.

39. Hagiwara M, Yamagishi Y, Hirai J, Koizumi Y, Kato H, Hamada Y, et al. Drug-induced hypersensitivity syndrome by liposomal amphotericin-B: A case report. BMC Res Notes 2015;8:510.

40. Groll AH, Rijnders BJ, Walsh TJ, Adler-Moore J, Lewis RE, Brüggemann RJ. Clinical pharmacokinetics, pharmacodynamics, safety and efficacy of liposomal amphotericin B. Clin Infect Dis 2019;68(4 Suppl 4):S260-74.

41. Soares JR, Nunes MC, Leite AF, Falquete EB, Lacerda BE, Ferrari TC. Reversible dilated cardiomyopathy associated with amphotericin B therapy. J Clin Pharm Ther 2015;40:333-5.

42. Nett JE, Andes DR. Antifungal agents: Spectrum of activity, pharmacology, and clinical indications. Infect Dis Clin North Am 2016;30:51-83.

43. Andrew EC, Curtis N,Coghlan B, Cranwicz N, Gwee A. Adverse effects of amphotericin B in children; a retrospective comparison of conventional and liposomal formulations. Br J Clin Pharmacol 2018;84:1006-12.

44. Solomon M, Schwartz E, Pavlotsky F, Sacka N, Barzilay A, Greenberger S. Leishmaniasis (PKDL). PLoS One 2017;12:e0174497.

45. Brüggemann RJ. Clinical pharmacokinetics, pharmacodynamics, safety and efficacy of liposomal amphotericin B. Clin Infect Dis 2019;68(4 Suppl 4):S260-74.

46. Pilmis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: An updated review. J Antimicrob Chemother 2015;70:14-22.

47. Amphotericin B: In: Drugs and Lactation Database (LactMed). Bethesda (MD): National Library of Medicine (US); 2021.

48. Renal dosage adjustment guidelines for antimicrobials. Available from: https://www.unmc.edu/intmed/divisions/id/asp/news/docs/antimicrobial-renal-dosing-guidelines.pdf. [Last accessed on...
Ambisome (amphotericin B) liposome for Injection. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050740s016lbl.pdf. [Last accessed on 2021 Nov 05].

Carolus H, Pierson S, Lagrou K, Van Dijck P. Amphotericin B and other polyenes-discovery, clinical use, mode of action and drug resistance. J Fungi (Basel) 2020;6:321. doi: 10.3390/jof6040321.

Vincent BM, Lancaster AK, Scherz-Shouval R, Whitesell L, Lindquist S. Fitness trade-offs restrict the evolution of resistance to amphotericin B. PLoS Biol 2013;11:e1001692.

Sanglard D, Ischer F, Parkinson T, Falconer D, Bille J. Candida albicans mutations in the ergosterol biosynthetic pathway and resistance to several antifungal agents. Antimicrob Agents Chemother 2003;47:2404-12.

Posch W, Blatzer M, Willflingseder D, Lass-Flörl C. Aspergillus terreus: Novel lessons learned on amphotericin B resistance. Med Mycol 2018;56(suppl_1):73-82.

Seo K, Akiyoshi H, Ohnishi Y. Alteration of cell wall composition leads to amphotericin B resistance in Aspergillus flavus. Microbiol Immunol 1999;43:1017-25.

Mesa-Arango AC, Rueda C, Román E, Quintin J, Terrón MC, Luque D, et al. Cell wall changes in amphotericin B-resistant strains from Candida tropicalis and relationship with the immune responses elicited by the host. Antimicrob Agents Chemother 2016;60:2326-35.