



# Liposomal Amphotericin B Usefulness in Critical Care Unit: A Review Study

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## Abstract

During the last 3 decades, the prevalence and variety of invasive fungal infections increased, especially in the critically ill patients thanks to advances in medical sciences, modification of the instruments, drugs, and protective-therapeutic methods. Such infections are administered by 4 pharmaceutical classes as follows: 1. Polyenes; 2. Azoles; 3. Echinocandins; 4. Pyrimidine analogues. One of these drugs is polyenes consisting of amphotericin and its lipid-based formulation. The lipid formulation of this drug is used due to its fewer side effects compared with the conventional type of the drug that makes it possible to enhance the drug efficacy by increasing the administered dosage. This pharmaceutical class is used to treat the following diseases in the critically ill patients: candidiasis, invasive aspergillosis, mucorales infection, cryptococcal meningoencephalitis, visceral leishmaniasis, persistent fever and neutropenia, renal replacement therapy (RRT) in intensive care unit (ICU), kidney transplantation, and liver problems. Now, the World Health Organization (WHO) approved liposomal amphotericin B (AmB) as the first-line treatment of visceral leishmaniasis in the Eastern Africa. It was even used with a single dose of 10 mg/kg with 95% efficacy. The current study aimed at investigating the effect of amphotericin and its lipid formulation to treat the aforementioned diseases.

## 1. Introduction

The prevalence and variety of invasive fungal infections increased over the last 3 decades due to the following reasons:

Changes occurred in the medical care and surgery, especially in the ICU, including the use of invasive catheters to monitor the patients, the use of agents and drugs that weaken the immune system, long-term treatment with wide-range ABs (1), the use of protective methods such as ventilator, hemodialysis, venous hemofiltration, hyperalimentation, and the use of antineoplastic and transplantation (of organs and bone marrow) therapeutic methods in patients with liver, kidney, and cardiopulmonary diseases in their background. Due to these medical advances and therapeutic achievements, the population at risk for fungal infections considerably increased and resulted in a change in the approaches adopted toward fungal infections (2, 3).

Today, systemic fungal infections are among the serious problems, especially in the intensive care units (ICUs) because many of the critically ill patients have a weak immune system due to the reasons mentioned above (4, 5). Invasive fungal diseases are the important reasons in the

mortality and morbidity of the patients with immune deficiency and are also related to the increased health care costs (6). Now, fungal infections, especially candidiasis and aspergillosis, are considered as new health problems in the critically ill patients including those receiving transplants (7).

There were many advances in the antifungal treatments over the last decades. The 4 categories of antifungal drugs used to treat the critically ill patients with invasive fungal infections include polyenes, azoles, echinocandins, and pyrimidine analogues.

The functioning of the polyenes category is investigated here:

### 1.2. Polyenes (amphotericin B)

The deoxycholate AmB is used as the main medicine to treat the invasive fungal infections for a number of decades. This drug covers a wide spectrum of fungal infections. Table 1 presents the efficacy of this pharmaceutical class in different fungal species.

The AmB has fungicidal effects and its efficacy is based on the drug capacity to link with ergosterol, and the main sterol constituting the cell membrane. It disturbs osmotic

**Table 1.** Pathogenic Fungi and Polyenes (7)

Microorganism	Polyenes Activity	Microorganism	Polyenes Activity
<i>Candida albicans</i>	1st-line	<i>Aspergillus fumigates</i>	2nd-line
<i>Candida glabrata</i>	2nd-line	<i>Aspergillus terreus</i>	No activity
<i>Candida tropicalis</i>	1st-line	<i>Fusarium</i> sp.	2nd-line
<i>Candida parapsilosis</i>	1st-line	<i>Scedosporium apiospermum</i>	Unknown
<i>Candida krusei</i>	2nd-line	<i>Scedosporium prolificans</i>	Unknown
<i>Candida guilliermondii</i>	2nd-line	<i>Trichosporon</i> spp.	3rd-line
<i>Candida Lusitaniae</i>	2nd-line	Zygomycetes (e.g., <i>Lichtheimia</i> ., <i>Macor</i> ., and <i>Rhizopus</i> spp.)	1st-line
<i>Cryptococcus neoformans</i>	1st-line	Dematiaceous molds (e.g., <i>Alternaria</i> , <i>Bipolaris</i> , <i>Curvularia</i> , and <i>Exophiala</i> spp.)	3rd-line
<i>Aspergillus flavus</i>	2nd-line	Dimorphic fungi:	
		<i>Blastomyces dermatitidis</i>	1st-line
		<i>Coccidioides immitis</i>	1st-line
		<i>Histoplasma capsulatum</i>	1st-line
		<i>Sporothrix schenckii</i>	1st-line

equilibrium in the cell membrane, increases the permeability of the cell membrane and consequently results in the subsidence of the cell ingredients and the death of fungal cells (7-9).

In spite of the long usage of this drug, no considerable resistance to this pharmaceutical class is observed, except in the following cases:

*C. glabrata* and *C. krusei* need higher degrees of MICs (minimum inhibitory concentrations) (10) and filamentous fungi (*Aspergillus* species) have higher resistance compared with polyenes (11). The use of conventional AmB is restricted due to the narrow therapeutic window and its side effects, specifically the nephrotoxicity (12). The danger of nephrotoxicity increases when it coincides with other nephrotoxic drugs such as aminoglycosides, antineoplastic drugs, cidofovir, cyclosporine, Foscarnet and pentamidine (13). The nephrotoxicity is a progressive disorder in kidney functions related to hypokalemia, tubular acidosis, and hypocalcemia (7). Another major problem of injecting AmB is its side effects including fever and chills, headache, myalgia and rigors. To decrease these side effects, slow infusion and infusion with acetaminophen and hydrocortisone are recommended (14).

Some lipid forms of the drug AmBs decrease the problems caused by conventional type of the drug. These formulations include (14-16)

- Liposomal amphotericin B (Lip AmB)
- Amphotericin B lipid complex (ABLC)
- Amphotericin B colloidal dispersion (ABCD)

The lipid-based formulations of the amphotericin have fewer nephrotoxic effects than the conventional type (7). Their effect is same as that of the conventional type (14, 15). However, they have a better safety profile (17) and the reac-

tions/side effects of AmB infusion are less severe and less frequent in the lipid formulations of this drug (14). Nevertheless, the lipid formulations are more expensive than the conventional type (7, 13). The combination of AmpB with liposomes results in a decreased interaction of AmpB with the mammals' cells while maintaining the multifungal property of the drug (18). Various studies showed a good clinical tolerance of Lip AmB (19-22). The liposomal type decreases the side effects such as fever and chills and protects against nephrotoxicity (23). Due to the low degree of Lip AmB toxicity, the drug dose can be considerably increased, which result in the increased efficacy of the drug (24, 25). However, side effects such as anemia, thrombocytopenia, nephrotoxicity, and hepatotoxicity are reported for Lip AmB and the first 2 side effects are dose-limited (26). Nevertheless, it seems that Lip AmB has less degrees of toxicity compared with the other 2 lipid formulations (13). The contraindication to this pharmaceutical class is hypersensitivity to AmpB and there is a possibility of anaphylaxis (7). The major side effects and the interactions of this pharmaceutical class can be observed in Table 2. Notice that this pharmaceutical class does not intervene in a cytochrome P450-dependent pathway (7).

The type and dose of polyene pharmaceutical class are shown in brief in Table 3 (7).

The role of polyenes (amphotericin and its lipid formulations) in the control of fungal infections:

#### 1. *Candida* spp.

In contrast to the 2004 guideline, the 2009 IDSA guideline (infectious disease society of America) introduces the AmB and its lipid formulations as alternative therapy for candidemia (28). Such a change is due to the fact that this pharmaceutical class is nephrotoxic (29). However, in a

**Table 2.** Polyenes Major Side Effects and Interactions

Polyenes	Major Side Effects	Drug Interactions
<b>1) Amphotericin B</b>	Nephrotoxicity, infusion-related reaction, pain at the site of injection, phlebitis, thrombophlebitis, cardiopulmonary (cardiac arrest, hypotension, tachypnea, and arrhythmia) anemia, thrombocytopenia, leukopenia, coagulation defect, anorexia, nausea, diarrhea, generalized pain, muscle, joint pain, headache, anaphylactic reaction, bronchospasm, wheezing, rash, acute liver failure, hepatitis, jaundice, convulsion, and hearing loss	Antineoplastic agents, corticosteroids and corticotrophin, digitalis glycosides, flucytosine, azoles, other nephrotoxic medications, skeletal muscle relaxants, and leucocyte transfusion
<b>2) Liposomal amphotericin B</b>	Infusion related reaction, renal toxicity, chest pain, hypotension, tachycardia, diarrhea, nausea, vomiting, abdominal pain, bilirubinemia, liver enzymes elevation, hypokalemia, hypomagnesemia, anxiety, headache, lung disorder, pleural effusion, and rash	Same as above
<b>Amphotericin B colloidal dispersion</b>	Infusion-related reaction, renal toxicity, hypotension, tachycardia, abdominal pain, hypokalemia, diarrhea, nausea vomiting, rash, dyspnea, asthma, confusion, and dizziness, cardiac toxicity <sup>a</sup>	Antineoplastic agents, corticosteroids and corticotrophin, digitalis glycosides, and azoles
<b>Amphotericin B lipid complex</b>	Infusion-related reactions, increased serum creatinine, cardiopulmonary (hypotension, tachypnea, arrhythmia, pleural effusion, anaphylactic reaction (bronchospasm, wheezing, and asthma), rash, acute liver failure, hepatitis, jaundice, nausea vomiting, abdominal pain, headache, renal toxicity dosedependent, muscle, joint pain, convulsion, and tinnitus	Same as above

<sup>a</sup>Cardiac toxicity is a rare phenomenon that results in AV block through an unknown mechanism that can be attributed to the change by the drug in the depolarization of the myocardial membrane (27).

**Table 3.** Principle Indications of Polyenes and dosing Schedule

Agent	Indications	Dosing Schedule
<b>Amphotericin B</b>	Invasive fungal infections include aspergillosis, cryptococcosis, North American blastomycosis, systemic candidiasis, coccidioidomycosis, histoplasmosis, and zygomycosis, as well as <i>Conidiobolus Basidiobolus</i> species, and <i>Sporotrichosis</i> .	0.3 - 1.5 mg/kg
<b>Liposomal amphotericin B</b>	Empirical therapy in patients with febrile neutropenic Cryptococcal meningitis in patients with HIV Visceral leishmaniasis	3 mg/kg/day; 6 mg/kg/day; 3 - 4 mg/kg/day
<b>ABCD</b>	No primary indication; only salvage therapy	3 - 6 mg/kg
<b>ABLC</b>	No primary indication; only salvage therapy	5 mg/kg

number of studies it is stated that in case preventive factors such as enough hydration by means of normal saline, electrolytes replacement and continuous drug infusion occur, the nephrotoxicity is not considered an issue and the efficacy of this drug remains the same as that of the new generation of drugs (7, 30). Yet, it should be noted that prehydration can be problematic in the patients receiving transplants because people with nephron and liver problems usually have volume overload and a low level of serum

albumin that can result in patients' experiencing a pulmonary reaction similar to pulmonary edema while receiving AmpB and its lipid formulations (31).

To treat candidemia and the documented invasive candidiasis in non-neutropenic patients, based on the following guidelines, the AmpB and its lipid formulations were selected as alternative therapy (13):

1. IDSA (28)
2. European society of clinical microbiology and infec-

tious disease (ESCMID) (32)

3. European expert opinion (33)

4. Canadian clinical practice guidelines for invasive candidiasis in adults (34)

5. Joint recommendation of German speaking mycological society (35)

Based on the IDSA guideline, AmB and its lipid formulations along with fluconazole, echinocandins, and voriconazole are among the therapeutic choices for candidiasis in the ICU (28) and they are selected as an alternative therapy under the following conditions: resistance to fluconazole and echinocandin, resistant infections or infections suspicious of having other pathogens (except for *Candida* spp.) such as *Cryptococcus* spp. (29).

According to ESCMID 2011 guideline, it is advised to use echinocandins in invasive *Candida* infections, as the first choice before Lip AmB (the second selection) and fluconazole (the third selection) (29). However, in the official statement of the American society, it is stated that in invasive *Candida* infections, in the case of hemodynamic instability, the AmB, Lip AmB, echinocandins, voriconazole, or a high-dose fluconazole should be administered (36).

The German speaking mycological society and the Paul-Elrich society advise the administration of echinocandins and Lip AmB for critically ill and septic patients with invasive *Candida* infections (35).

With regard to the mentioned guidelines, the algorithm 1 (Figure 1) is suggested to treat patients with invasive *Candida* infections in ICU (13).

A combination of AmB and flucytosine is suggested to treat localized candidiasis infections such as meningitis, osteomyelitis, and intra-abdominal *Candida* infections (35). Table 4 presents the therapeutic dose and the therapy duration for the localized invasive *Candida* infections.

## 2. Invasive Aspergillosis

Invasive aspergillosis is the most important invasive fungal disease in patients with weakened immune systems. There is a 10% probability of its occurrence in allogeneic bone marrow transplant receivers (37) and a 58% mortality probability (43.87% dependent on the underlying disease) (38). Therefore, compared with patients without aspergillosis, patients with aspergillosis need longer hospitalization and higher therapeutic costs (39, 40). Due to its great importance, even in the case of clinical suspicion to invasive pulmonary aspergillosis, the antifungal therapy should begin. In the past, AmB was used to treat invasive fungal infections. However, reports of aspergillosis' resistance to this drug and its side effects restricted the application of this drug (41) and today, voriconazole and lipAmB are used to treat invasive fungal diseases such as invasive aspergillosis (39). A combination of these 2 drugs

cannot be used because it causes antagonistic effects (42). It is approved that the lipid formulations of AmB can be used as a salvage therapy in the invasive pulmonary aspergillosis with a dose of 3-5 mg/kg/day, and although the high dose of these formulations (10 mg/kg/day) is as effective as the low dose, there is a higher probability of poisoning (43). It is observed that in the critically ill patients, a combination of AmB lipid formulations with echinocandins can be effective to treat the invasive aspergillosis (44).

## 3. Mucorales Infection

Upon the diagnosis of the mucorales infection, the Lip AmB usage should begin with 5-10 mg/kg/day. If the intracerebral is infected too, the maximum dose should be used. As the second line of treatment, posaconazole can be used twice a day, with a dose of 400 mg. This drug can be used in combination with Lip AmB. It should be noted that besides the mentioned drug therapy, the treatment of mucor needs surgery interventions and the treatment of underlying medical problems.

## 4. Cryptococcal meningoencephalitis

Cryptococcal meningoencephalitis is a fatal opportunistic infection. The global burden of this disease is related to the epidemics of HIV/AIDS especially in the sub-Saharan in Africa (45). It also occurs in other patients with immune deficiency including the solid organ transplant receivers and the therapy consists of an intense period of treatment including AmB formulations (46). The lipid formulations of amphotericin are known as the first line of the treatment of cryptococcal meningoencephalitis (47).

According to IDSA, it is suggested that Lip AmB with or without flucytosine be used to treat cryptococcal meningitis resulted from HIV/AIDS. In addition, a combined therapy is recommended for the patients undergoing transplantation. So far, different therapeutic regimes are defined to treat this infection including (46).

1. Lip AmB 6 mg/kg/day

2. Lip AmB 3 mg/kg/day + flucytosine 50 mg/kg/day

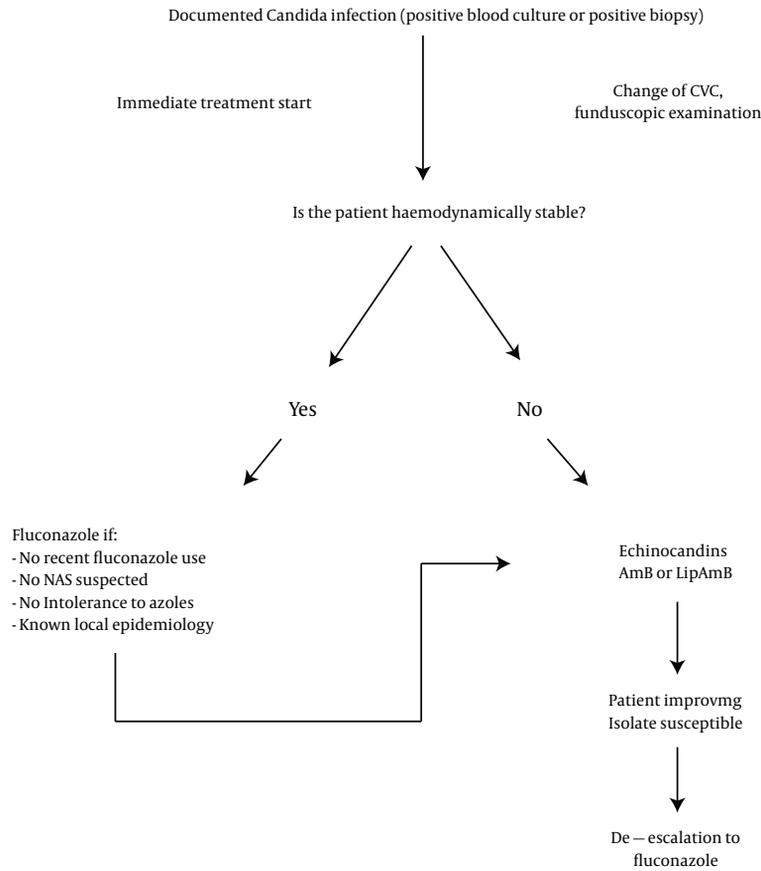
3. Lip AmB 3 mg/kg/day + flucytosine 100 mg/kg/day

Among the mentioned regimens, the regimen number 2 had the highest antifungal effects and the least toxicity compared to the other doses (47).

## 5. Visceral leishmaniasis

Visceral leishmaniasis, also known as Kala-Azar, is a parasitic life-threatening disease (protozoan parasite). The agent creating it is *Leishmania donovani* that is transferred by the phlebotomus, usually observed in the tropical regions (48). Visceral leishmaniasis is the second fatal parasitic disease after malaria and it afflicts 200,000 to 400,000 people annually (49). Over 90% of visceral leishmaniasis cases are observed in India, Bangladesh, Nepal, Brazil, South Sudan, and Ethiopia (49), half of which live

**Figure 1.** Suggested Treatment Algorithm for Patients with Invasive Candidiasis Admitted to ICU



(NAS: non- albicans species, CVC: central venous catheter, AmB: amphotericin B, LipAmB: liposomal amphotericin B).

**Table 4.** Recommended Dose of AmB and Liposomal AmB for the Localized Forms of Invasive Candidiasis According to 2009 IDSA Guidelines<sup>a</sup>

Infection Type	Suggested Treatment	Infection Type	Suggested Treatment
<b>Pyelonephritis</b>	AmB 0.3 - 0.6 mg/kg/d for 1- 7 days	CNS infection	Lip AmB 3 - 5 mg/kg (± 5FTC 25 mg/kg/qid) several weeks, then fluconazole (6 - 12 mg/kg/d)
<b>Urinary fungus ball</b>	Surgical removal recommended AmB 0.5 - 0.7 mg/kg/d	Endocarditis	Lip AmB 3 - 5 mg/kg (± 5FTC 25 mg/kg qid) or AmB 0.6 - 1 mg/kg/d (± 5FTC 25 mg/kg) or echinocandin
<b>Candida osteomyelitis</b>	Lip AmB 3 - 5 mg/kg/d (weeks), then fluconazole for 6 - 12 months	Supportive thrombophlebitis	Lip AmB 3 - 5 mg/kg/d or echinocandins
<b>Septic arthritis</b>	LipAmB 3 - 5 mg/kg/d (weeks), then fluconazole	Endophthalmitis	AmB 0.7 - 1 mg/kg plus 5FTC or Lip AmB 3 - 5 mg/kg/d (or voriconazole or echinocandins)

<sup>a</sup>It should be noted that in all of the above cases, except for the endocarditis, fluconazole can also be used singly as a therapeutic selection.

in India (50).

The parasite migrates to internal organs such as liver, spleen, and bone marrow and leads to persistent fever, hepatosplenomegaly, severe anemia, and a severe damage to

the host's immune system (48). In case it is not cured, almost always it leads to death, most often after a secondary opportunistic infection such as pneumonia, tuberculosis and dysentery (51). Since no effective method is known to

control the carrier phlebotomus, the point to count on in the disease control is to find patients and treat them (52). During the recent decades, the treatment of this disease is based on the intramuscular (IM) injection of antimonial (48). Although these drugs are effective, they have a high degree of toxicity and in complicated cases, and result in mortality (53). Treatment with these drugs needs long hospitalization and in some regions such as India, the disease is resistant to them (48).

Lip AmB is a drug with high application and low toxicity and at present, it is considered as the preferred therapy to treat visceral leishmaniasis in high-income countries (54). Moreover, it was recommended and approved by the world health organization (WHO) as the first-line drug for visceral leishmaniasis in the East Africa since 2010 (51). Lip AmB is also used in cases of complicated initial visceral leishmaniasis and in the relapse of visceral leishmaniasis and in patients with the contraindication of paromomycin and antimonial agents (51). It seems that despite being expensive, Lip AmB is safe to treat visceral leishmaniasis (51).

Lip AmB 20 mg/kg was used in India to treat patients with visceral leishmaniasis. The drug was used with 4 doses of 5-mg/kg for 4-10 days dependent on patient's clinical situation and the severity of the disease; therefore, patients with more severe situations spent a 10-day treatment period (50, 51). The AmB deoxycholate IV is the 2nd-line drug because it needs a longer hospitalization (around 30 days) and has greater toxicity than its lipid forms (55). The ABLC, however, provides the possibility that a higher dose of the drug be prescribed to patients by a safer and shorter method (56). Despite being expensive, in a 6-month follow-up it was observed that it had a lower relapse and was safe and effective (50).

There is also another therapeutic method for this drug. In this method, Lip AmB was used with a single dose of 10 mg/kg that was safe and had over 95% efficacy (57). As mentioned above, Bangladesh is among the countries with a high prevalence of visceral leishmaniasis. Here, a single dose of Lip AmB is used as the safest and the most effective therapy for visceral leishmaniasis. A research carried out in this country revealed that Lip AmB received the highest degree of satisfaction among patients and hospital staff. Moreover, a single dose of this drug has the fewest side effects and reduces the treatment costs. Before the prescription of Lip AmB in Bangladesh, the oral drug of miltefosine was used as the 1st-line treatment of visceral leishmaniasis replaced by Lip AmB due to the advantages presented in Table 5 that led to its superiority to miltefosine and turned it to the 1st-line treatment of visceral leishmaniasis (58).

The single-dose Lip AmB (Slip AmB) is better tolerated and only has some minor side effects such as a mild and

short fever upon infusion. Patients receiving this drug indicated a quick recovery and besides satisfaction to use it, they preferred a single-dose infusion to a 28-day use of the pills. Other positive points of using Slip AmB include its 100% adherence rates and the fact that this drug can be safely used in pregnancy (60).

Some problematic issues in the use of Lip AmB include the necessity for trained forces, infusion instruments and equipment, and the measurement of hemoglobin and other clinical parameters. Moreover, this drug needs some equipment for its special storage conditions to ensure that the drug temperature does not exceed 25°C (58).

#### 6. Persistent Fever and Neutropenia

Invasive fungal infections are among the important factors creating illness and death in patients with neutropenia under chemotherapy and patients undergoing the transplant of hematopoietic stem cell (61-63).

In such people, the degree of infections resulted from invasive and opportunistic fungal infections is 10% to 25%, the degree of mortality resulted from the invasive candidiasis is 35% to 50%, and the degree of mortality resulted from invasive aspergillosis and other invasive fungal filaments is 65% to 90% (63, 64). A persistent fever in patients with neutropenia receiving a wide range of antibiotics can be the only clinical symptom of invasive fungal infections (65).

Lip AmB and caspofungin are both important factors to treat invasive fungal infections in the mentioned patients (66).

AmB and its lipid formulations are used as antifungal empirical treatments against many opportunistic fungal infections in patients with persistent fever and neutropenia (65, 67, 68).

The drug dose chosen for the antifungal experimental treatment of patients with persistent fever and neutropenia was 3 mg/kg of Lip AmB (69).

Caspofungin is also effective against candidiasis and aspergillosis (65, 70-72) and despite some clinical restrictions, both drugs are used in combination to treat patients with fulminant and recurrent infections, infections in organs that are difficult to treat and infections with agents decreasing the reaction to antifungal factors (70, 73, 74). Except for a greater hypokalemia observed in the combination therapy of caspofungin and Lip AmB, similar to monotherapy, combination therapy is safe and no interaction is observed between these 2 drugs (66).

#### 7. The Efficacy and Role of Lip AmB in Patients in Need of Renal Replacement Therapy in ICU

In recent years, there was an increased use of RRT in the hospitalized and critically ill patients in ICU. Although in most of the cases RRT is used in patients with acute re-

**Table 5.** Patients' Experiences and Perceived Benefits by the SLip AmB and Miltefosine Treatment Regimen<sup>a</sup>

Indicator	SLip Am N = 299	Miltefosine N = 22	P Value
Resolution of fever in days	2.48 ± 0.86	17.58 ± 11.34	< 0.001
Nausea/vomiting after treatment	1.3 (4)	86.4 (19)	< 0.001
Diarrhea	0.00 (0)	63.6 (14)	< 0.001
Abdominal pain	0.7 (2)	27.3 (6)	< 0.001
Mean of time to recovery in days	2.39 ± 0.731	17.36 ± 12.385	< 0.001
Mean of time in days to start working after treatment	2.72 ± 1.819	52.82 ± 33.987	< 0.001
Income-loss due to recovery time	2.72 days × 0.30 <sup>b</sup> /day = 0.816\$	52.82 days × 0.30\$/day = 15.846\$	< 0.001
Income-loss (working days lost when receiving treatment)	2.39 days × 0.3\$/d = 0.72\$	17.36 days × 0.3\$/d = 5.2\$	< 0.001

<sup>a</sup>Values are expressed as mean ± SD or % (No.).

<sup>b</sup>Average daily income per person in a visceral leishmaniasis affected household in Bangladesh, calculated by Anoop Sharma et al. 2006 (59).

nal failure (uremia and metabolic acidosis) to modify the functioning of the kidneys, it is prevalently used to treat other situations such as anasarca (generalized edema), electrolyte disorders, acute intoxication, acute pulmonary edema, and even severe sepsis (75).

The use of RRT can influence the concentration of azoles (76, 77). The administration of echinocandins (78, 79) and polyenes (80, 81), however, has the least degree of change. Therefore, it is not required to monitor plasma concentration and the dose changes in such cases (16, 75); and the clinical efficacy of Lip AmB in patients in need of RRT is similar to that of patients with no need to RRT (75).

Table 6 provides a general presentation of the effects of the polyenes class on the kidneys.

#### 8. The Effects of AmpB Formulations in Patients Receiving Liver Transplants and Patients with Liver Problems

Patients receiving liver transplants, especially those who need more than 5 days of hospitalization in ICU, are patients with high risks of afflicting with invasive liver infections (82). Invasive fungal infections upon liver transplant bring about a high degree of mortality and the conducted research showed that there was 18% to 42% probability of the occurrence of invasive fungal infections and resulting 50% to 78% of mortality in these patients (83-88). Here, *Candida* spp. is responsible for the majority of infections. However, many of the patients with candidiasis survive while infections created by *Aspergillus* spp. are almost fatal (84, 85, 88). The prophylaxis with fluconazole in patients with high risks of invasive fungal infections reduces the occurrence of invasive candidiasis (89). However, there is the possibility of fungus resistance to fluconazole and failure in the prevention from invasive aspergillosis (90). Although fluconazole decreases fungus colonization and the mortality resulted from invasive fungal infections, in general, it improves the patients' survival (91).

AmpB formulations are considered as a choice agent for the prophylaxis of fungal infections resulted from aspergillosis. However, the toxicity resulted from conventional AmpB has limited its use as an antifungal prophylaxis in the liver transplant receivers and has resulted in the prohibition of its use in the liver transplant receivers (92). Generation of lipid-based formulations of amphotericin that are less toxic than the conventional type has led to a higher tendency to use such lipid-based formulations as a prophylaxis (93-96).

Among these lipid forms, ABLC is a lipid form with a high proportion of amphotericin-lipid (1:1) that creates a low plasma concentration, but has greater tissue levels than other lipid formulations of AmpB (97).

The ABLC is as effective as the conventional type, but it has less toxicity in people with invasive candidiasis and immune deficiency (98).

To have the antifungal prophylaxis in liver transplant receivers, the use of ABLC (Abelect) with a dose of 1 mg/kg/day begins 5 days after the transplantation surgery and continues by the time of the patient's hospitalization in the ICU. The prophylaxis with ABLC in patients in need of long hospitalization in ICU after the transplant is tolerated well and prevents the fungal infections (82).

In patients with a liver disease background, the use of amphotericin and its lipid formulations increases the liver enzyme. Table 7 presents the doses related to the mentioned formulations for such patients.

### 3. Conclusions

Studies conducted to-date indicate the effective role of amphotericin B and its lipid formulations to treat invasive fungal diseases in the critically ill patients.

**Table 6.** Experience in Patients With a Preexisting Renal Disease

Agent	Effects on the Kidney	Dosing Modification for Preexisting Renal Disease
<b>Amphotericin B</b>	Nephrotoxic-elevation of BUN, Creatinine	Sodium loading to ameliorate toxicity
<b>Liposomal AmB</b>	Nephrotoxic	Used in patients with preexisting renal impairment
<b>ABCD</b>	Nephrotoxic	
<b>ABL</b>	Dose-limited renal toxicity	

**Table 7.** Experience in Individuals With Preexisting Hepatic Disease

Polyenes	Normal Patients	Mild (Child-Pugh 5 - 6)	Moderate (Child-Pugh 7 - 9)	Severe (Child-Pugh > 9)	Effects on the Liver
<b>Deoxycholate amphotericin B</b>	0.6 to 1 mg/kg/d	Data were not sufficient to determine dosing			Elevation of liver enzymes
<b>Amphotericin B lipid complex</b>	5 mg/kg/d	Data were not sufficient to determine dosing			Elevation of liver enzymes
<b>Amphotericin B colloidal dispersion</b>	3 - 4 mg/kg/d can be increased up to 6 mg/kg/d	Data were not sufficient to determine dosing			Elevation of liver enzymes
<b>Amphotericin B liposomal</b>	3 - 4 mg/kg/d can be increased up to 6 mg/kg/d	Data were not sufficient to determine dosing			Elevation of liver enzymes

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