mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Review article

Continuous infusion of amphotericin B deoxycholate: an innovative, low-cost strategy in antifungal treatment

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Summary

The combination of amphotericin B and sodium deoxycholate is the formulation most used in clinical practice. The development of new agents such as amphotericin with lipid formulations, caspofungin, voriconazole and other azolic derivatives, promoted alternatives to amphotericin B deoxycholate. However, because of the high cost of these new drugs, their use is difficult in a scenario of limited resources. A few strategies have been devised to make the use of amphotericin B deoxycholate less toxic. In this review, we seek to describe the accumulated knowledge about this molecule, with focus on its use in continuous infusion, which appears to be an alternative to reduce toxicity, while maintaining its clinical efficacy.

Key words: Amphotericin B deoxycholate, continuous infusion, low cost, toxicity, nephrotoxicity, efficacy.

Introduction

The significant increase in the number of patients with immunosuppressive conditions in the last few decades has resulted in a corresponding increase in the frequency of fungal infections. The prolonged survival of patients with neoplasms, transplants of solid organs and bone marrow cells, HIV/AIDS and chronic use of immunosuppressive medications are examples of these conditions. The growing importance of systemic mycoses in this context shows the need to learn more about the diagnosis and treatment of these conditions.

The difficulty to diagnose and the high mortality associated with systemic mycoses make empirical or even prophylactic treatments necessary. Amphotericin B deoxycholate is presently the most important of antifungal agents especially in institutions of healthcare settings with limited resources. However, considerable toxicity is frequently associated with its use, especially in the kidneys.[1–3]

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The development of new agents such as amphotericin with lipid formulations, echinocandins, voriconazole and other azolic derivatives promoted alternatives to amphotericin B deoxycholate. However, because of the high cost of these new drugs, their use is difficult in a scenario of limited resources. For instance, a daily dose of 5 mg kg^{-1} of liposomal amphotericin B for a patient of 70 kg body weight is 22 times more expensive than a daily dose of 1 mg kg^{-1} of amphotericin B. Furthermore, the benefit of these alternatives in most situations appears to be the decrease in toxicity and improved clinical response, but probably comparable with amphotericin B deoxycholate in terms of microbiological efficacy.[4–6]

Although there is much experience in using this drug and it has been available on the market for a long time, there is as yet no consensus on the ideal way of administering amphotericin B deoxycholate. A few strategies have been devised to make its use less toxic, such as sodium loading and use of premedications to avoid infusion-related toxicities. In this review, we seek to describe the accumulated knowledge about this molecule, with focus on its use in continuous infusion, which appears to be an alternative to reduce toxicity.[7]

Amphotericin B deoxycholate

Amphotericin B is a polyene antibiotic, which was isolated for the first time in 1959 from *Streptomyces*

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nodosus cultures. The strain was collected in 1944 in the Orinoco Delta, in Venezuela. The substance is still being extracted from cultures on an industrial scale. It is considered a non-aromatic polyene antimycotic.

All polyenes are characterised by low solubility. This low solubility explains why little or no gastrointestinal absorption of amphotericin occurs, and hence there is very low bioavailability when administered orally. Therefore, the drug is usually administered intravenously, mixed with a solubilising agent such as sodium deoxycholate.[8] The combination of amphotericin B and sodium deoxycholate is the formulation most used in clinical practice worldwide, especially in underdeveloped countries.

Amphotericin deoxycholate B is generally used to treat systemic and invasive fungal infections such as those caused by species of *Candida, Aspergillus, Fusarium, Zygomycetes, Trichosporon* and *Cryptococcus*. Besides being essential for the treatment of fungal infections, it is also the most important second-line drug to treat visceral and cutaneous leishmaniasis.[8]

Mechanism of action

Sterols are essential components of biological membranes and are responsible for the fluidity of the membrane. In mammalian cells, cholesterol is the predominant sterol, while in fungi, amoebas and protozoans of genus *Leishmania,* ergosterol is the major membrane component. The polyenic structure of amphotericin B allows it to form pores in the cellular membrane. In this context, amphotericin B strongly favours ergosterol compared with cholesterol. The polyenic chain interacts with the cholesterol or ergosterol molecule and the membrane phospholipids through the Van der Waals forces. The affinity of amphotericin B for cholesterol results in the potential toxicity against mammalian cells. Because of pore formation in the membrane, there is a loss in cellular integrity, resulting in rapid efflux of ions, especially potassium.[8]

Pharmacokinetics and pharmacodynamics

Gastrointestinal absorption of amphotericin B deoxycholate is minimal and detailed data remain fully unknown. Approximately 20–30% of amphotericin B is removed from the blood in the liver and excreted with bile in the faeces, and 2–5% of the amphotericin B deoxycholate found in the urine has not been metabolised and remains biologically active.[8] Bekersky *et al.* [9] found that two-thirds of the amphotericin B deoxycholate was excreted unchanged in the urine (20.6%) and faeces (42.5%) with >90% accounted for in mass balance calculations at 1 week, suggesting that metabolism plays at most a minor role in amphotericin elimination. When colloidal amphotericin B is admixed in serum, deoxycholate separates from amphotericin B and more than 95% of the latter binds to serum proteins. Most of the drug leaves the circulation and is stored in the liver and other organs. The concentration of amphotericin B in inflamed areas such as the peritoneum, pleura and joint is approximately two-thirds of the through serum level. Amphotericin B penetrates poorly into either normal and inflamed meninges, brain, saliva, bronchial secretions, vitreous humour, amniotic fluid, muscle and bone.[10]

The pharmacokinetic aim of any anti-fungal treatment is to reach therapeutic concentrations at the infection site. Thus, we must consider, besides medication, the causative fungus of the infection and its location or compartmentalisation. Most of the pathogenic fungi are present extracellularly, and therefore the serum concentration would be a reliable marker for appropriate therapy. However, in compartmentalised infections such as those of the central nervous system, like cryptococcal meningitis, the concentration in the brain parenchyma may be more important. In fact, animal studies have shown comparable and adequate penetration of different formulations of amphotericin B in the brain parenchyma.[7,11] In fact, treatment with amphotericin B deoxycholate (1 mg kg^{-1} day^{-1}) or liposomal amphotericin B (AmB) (5 mg kg^{-1} day^{-1}) yielded the highest peak plasma concentration [C(max)] and area under concentration. Amphotericin B deoxycholate and liposomal AmB had the greatest antifungal efficacy. This activity was concentration and time dependent.[9]

Pharmacodynamics establishes the relationship between pharmacokinetics and outcome. In the context of antimicrobials, the relationship between exposure to the drug and fungicidal activity or minimum inhibitory concentration (MIC) is considered. Thus, we have three parameters that are very useful to describe this relation, which are: (i) maximum serum concentration over the MIC (Cmax/MIC), (ii) the 24 h area under the curve divided by MIC (AUC/MIC), and (iii) the time during which the drug concentration is greater than MIC over a period of time, which is expressed as %/time/MIC (Fig. 1). Knowledge regarding which of these three parameters best describes the antifungal activity of a drug provides the basis to determine the frequency at which it can be most effectively administered. For instance, if Cmax/MIC is strongly correlated with the

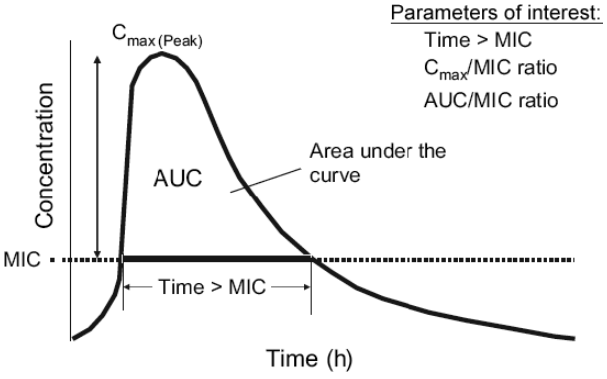

Figure 1 Pharmacokinetics of antimicrobial dosing relative to organism MIC. (From Andes D. Clinical pharmadynamics of antifungals. *Infect Dis Clin N Am* 2003; **17**: 635–49; with permission).

activity of drug A, the most appropriate therapeutic regimen would be high doses at prolonged intervals (concentration-dependent agent). On the other hand, if %/T/MIC describes drug activity most adequately, lower and more frequent doses or even continuous administration would be required to prolong the period during which the serum level of the drug is above MIC (time-dependent agent).[7]

Antifungals are not easily divided among time or concentration-dependent agents. Existing studies classify the polyenes such as amphotericin B deoxycholate as concentration-dependent compounds. However, there are conflicting results in these studies, as for instance, the antifungal action similar to that during the first few hours is persistent even after 24 h of administration, which may reflect *in vivo* the slow diffusion of these compounds into the tissues. Moreover, in a recent study evaluating the distribution of amphotericin B deoxycholate in its different formulations in the CNS of animal models, fungal eradication was associated with concentration-dependent parameters (Cmax/MIC), and the authors concluded that the antifungal activity was time and concentration dependent.[11,12] Although amphotericin B clearly has concentration-dependent activity, their is probably a ceiling effect of the free (bioactive) drug based on protein binding and drug solubility, which varies according to the site of infection such as in the kidney, lung, liver and brain. These considerations take into account only the microbiological eradication. However, in the case of a drug such as amphotericin B deoxycholate, which has major toxicity associated with it, as we will review below, it is important to value the importance of parameter %T/MIC in the treatment to sustain the feasibility of administering amphotericin B deoxycholate in a continuous infusion, a strategy that can reduce adverse effects. Even after 40 years of clinical use, the appropriate regime of amphotericin B deoxycholate has not yet been fully defined, and the manufacturer indicates a daily infusion of 2–6 h.

In vitro pharmacodynamics has shown that amphotericin B exhibited species-specific concentration-dependent activity with a ceiling effect of the bioactive drug, with 50% effective concentrations (EC_{50}s) ranging from 0.10 to 0.12 mg ml^{-1} for *Aspergillus fumigatus*, 0.36 to

Table 1 Reported studies describing the efficacy and decreased toxicity of continuous 24-h infusion of amphotericin B deoxycholate.

Reference	Study design	Infusion type compared	Number of patients	Diminished toxicity	Microbiological efficacy	Decreased mortality
Eriksson *et al.*	Prospective, randomised, [1]comparative Febrile neutropenia; haematological malignancy	4 h	86	Renal, infusional	Not shown	Yes
Uehara *et al.*	Retrospective, non-comparative; febrile, neutropenia; haematological malignancy	None	12	Renal	Not shown	yes
Speich *et al.*	Prospective, non-comparative; lung transplant Candida Pneumonia	None	6	Renal	Yes	yes
Peleg *et al.*	Prospective, comparative; febrile neutropenia haematological malignancy	4 h	77	Renal	Not shown	Yes
Furrer *et al.*	Retrospective; non-comparative febrile neutropenia; HSCT[1]	None	22	Renal	Not shown	Not shown
Altmannsberger *et al.*	Retrospective, comparative; febreile neutropenia, HSCT	6 h	7	Not shown	Not shown	Not shown
Schulenburg *et al.*	Prospective, comparative; febrile, neutropenic, haematological malignancy	2–6 h	17	Renal infusional	Not shown	Not shown
Falci *et al.*	Pilot, prospective, Non-comparative cryptococcosis and HIV	None	6	Renal, infusional	Yes	Not shown

[1]Haematological stem cell transplant.

0.53 mg ml^{-1} for *Aspergillus terreus*, 0.27 to ≥32 mg ml^{-1} for *Fusarium solani*, 0.41 to 0.55 mg ml^{-1} for *Fusarium oxysporum*, and 0.97 and 0.65 mg ml^{-1} for *Scedosporium apiospermum* and *S. prolificans*, respectively.[4] With regard to *Candida albicans*, similar optimal activity of amphotericin B may be achieved by maximising the peak drug concentration/MIC ratio.[15,16]

Toxicity

The toxicity of amphotericin B can be divided into acute (acute reactions to the infusion) and subacute effects (nephrotoxicity). Acute infusional reactions are characterised by symptoms such as chills, fever, nausea and vomiting, headache, hypotension, tachycardia and dyspnoea that occur during the administration of amphotericin B deoxycholate. These reactions often require medical attention and the use of medications such as dexchlorpheniramine or meperidine. Cases of severe cardiac arrhythmias have been already described during the administration of amphotericin B deoxycholate.[8,17]

The incidence of nephrotoxicity may reach levels between 49% and 65%; it may result in the significant loss of renal function and require dialysis. The use of other nephrotoxic drugs along with amphotericin B deoxycholate, and consequently, dialysis as a result of the loss of renal function were clearly associated with mortality.[3]

The pathophysiology of nephrotoxicity involves two mechanisms: severe vasoconstriction resulting in reduced renal blood flow and, consequently, the glomerular filtration rate (GFR); and direct interaction between amphotericin B deoxycholate and the membranes of the renal epithelial cells causing tubular dysfunction. These two mechanisms collectively determine the loss of renal function.[3] The two mechanisms interact in a tubuloglomerular feedback in which the low sodium concentration in the dense macula caused by proximal tubular dysfunction increases afferent vasoconstriction, further reducing renal blood flow.[18]

Potential risk factors for nephrotoxicity include the daily dose of amphotericin B deoxycholate received by the patient, dehydration, cumulative dose, duration of therapy over 2 weeks, abnormal baseline renal function and nephrotoxic drugs used concomitantly.[3] To detect nephrotoxicity, it is necessary to maintain clinical surveillance for the symptoms such as tubular dysfunction and renal failure. Hypokalaemia is a frequent complication of amphotericin B deoxycholate therapy, which requires potassium supplementation to maintain normal potassium levels. In a significant number of patients, amphotericin B deoxycholate will induce the changes including hypokalaemia, hypomagnesaemia, renal tubular acidosis and polyuria. There is a progressive increase in serum creatinine, and is usually reversible with the suspension of the drug; however, in cases of larger cumulative doses (above 4 g), it may be irreversible. Twenty-five per cent increase in serum creatinine should be considered as an evidence of a clinically significant decrease in the GFR.[3] Before and during treatment, hydration and increased urinary output are essential to prevent nephrotoxicity. In addition, sodium loading has been shown to prevent amphotericin B deoxycholate-induced nephrotoxicity.

Other adverse effects described include anaemia, neutropenia, thrombocytopenia and changes in the liver function tests. However, these side effects, especially anaemia, do not usually cause significant morbidity or mortality.[8]

Amphotericin B deoxycholate in a continuous infusion

Clinical studies

Considering the high cost of lipid amphotericin, strategies have been sought that allow the use of amphotericin B deoxycholate with a lower level of toxicity.[19] Based on the pharmacokinetic rationale that 4-h infusions will result in greater binding of plasma proteins, and higher serum levels than the 24-h infusions, with greater and faster distribution of amphotericin B deoxycholate in the tissues and consequently greater nephrotoxicity, studies with continuous infusion of amphotericin B deoxycholate for 24 h appears to be a promising strategy to diminish the associated nephrotoxicity, as shown in the Table 1. Moreover, the concept of the importance of the two parameters (Cmax/MIC and %T/MIC) together, for microbiological eradication, ensures the possibility and feasibility of using this strategy. In this way, the reduction of toxicity appears, at least partly, to depend on a lower release of amphotericin B deoxycholate into the tissues.[20] For instance, Chabot *et al.* [21] evaluated the role of continuous infusion of AmB over a period of 52–120 h in the biochemical modulation of antineoplastic agents administered in patients with advanced carcinomas. Therapeutic plasma levels of amphotericin B were rapidly reached and maintained for the duration of infusion, with a reduction in acute toxicities associated with shorter infusions. Biochemical modulation of antineoplastic

agents by continuous amphotericin B deoxycholate infusion was not demonstrated clinically.

Eriksson *et al.* [1] developed a randomised clinical trial comparing the 4-h infusion of amphotericin B deoxycholate (conventional) vs. 24-h infusion (continuous infusion). Eighty-six patients were enrolled with an indication to use amphotericin B, most of them febrile neutropenic with haematological malignancies. The study included and defined some patients with persistent fever and proven fungal infection, which included cryptococcosis (1), aspergillosis (4) and pulmonary Rhizopus infection (1) in the rapid infusion group and proved angioinvasive mould pulmonary infection (3) in the 24-h infusion group. A significant difference was found with respect to an increase in acute infusional reactions such as fever and chills in the patients who received a 4-h infusion. The patients who received a continuous infusion required lesser medications against infusional reactions. In addition, higher levels of serum creatinine were seen in the group that received the 4-h infusion. There were no differences in relation to hypokalaemia or hypomagnesaemia. The highest mortality rate (total of seven deaths in the study) was seen in the group that received the 4-h infusion. Despite a higher number of proved or probable fungal infections, there was no death in the continuous infusion group, whereas three patients died with proved fungal infections at necropsy in the rapid infusion group. Breakthrough fungaemia did not occur in any of the groups. The data on the efficacy in this study support the notion that continuous infusion of amphotericin B deoxycholate is at least as effective as the daily 4-h infusions. The reduction of acute infusional reactions in this study can be explained by the induction or slower release of inflammatory mediators such as C reactive protein during the continuous infusion of amphotericin B deoxycholate, which was comparable with the reduction observed in trials with lipid formulations. Comparing the ratio of peak serum creatinine with baseline creatinine concentrations during and at the end of treatment, the authors found a significantly higher ratio in the rapid infusion group. This marked reduction of nephrotoxicity observed in continuous infusion group is comparable with that observed in patients treated with liposomal amphotericin B. As no difference was observed in hypokalaemia, similarly to the studies with liposomal amphotericin B, the continuous infusion of amphotericin B deoxycholate appears to reduce mainly pretubular renal toxicity.[1,22]

A retrospective study analysed data from 12 patients with febrile neutropenia requiring antifungal therapy, who were treated with a 24-h continuous infusion of amphotericin B deoxycholate.[2] Only three of these patients presented proven fungal infection. No death occurred during the 7-day period analysed from the beginning of the administration of amphotericin B deoxycholate. The reduction in nephrotoxicity was similar to that observed in the study by Eriksson. Only four patients (30%) presented 1.5 times higher creatinine levels than the baseline. These findings were similar to the study by Walsh with liposomal amphotericin, where 29.40% of the patients were found to develop nephrotoxicity. Hypokalaemia and hepatotoxicity were frequent adverse effects as was expected, and as was also reported in other studies.[4] All patients survived for at least 7 days after starting continuous infusion of AmB-D, and clinical resolution occurred in 76% of the cycles. The authors concluded that amphotericin B deoxycholate was effective in continuous infusion; although there are limitations in the study (retrospective, small number of patients), the results were interesting and encouraged new clinical trials.

In patients who underwent lung transplant, Speich *et al.* [23] developed a pilot study using amphotericin B deoxycholate in continuous infusion. Six patients with semi-invasive bronchopulmonary azole-resistant candidal infections were enrolled in this small study. Once again, the results were satisfactory and the fungal infection was eradicated in five of the six patients, and the drug was well tolerated with the occurrence of nephrotoxicity in one patient (16%). These results also indicate that continuous infusion offers a real possibility of reducing the nephrotoxicity associated with amphotericin B deoxycholate without additional costs, especially in the context of the concomitant use of nephrotoxic drugs, as all the patients were using immunosuppressive agents that had proven nephrotoxicity, such as cyclosporine A.

The use of amphotericin B deoxycholate in a continuous infusion together with cyclosporine A was evaluated in patients submitted to allogenic transplant of bone marrow cells in a retrospective study conducted by Furrer *et al.* [24] As shown in previous studies, the authors concluded that the use of amphotericin B deoxycholate in continuous infusion was safe in patients who were receiving other nephrotoxic drugs.[17,19] The limitations of the retrospective study included a small number of patients analysed.

A retrospective cohort was analysed by Peleg *et al.* [25] which compared the infusion of amphotericin B in 4 h vs. continuous 24-h infusion. The patients had haematological malignancies, and required antifungal therapy. A dose of 0.6 mg kg^{-1} was used in patients

with febrile neutropenia and 1.0 mg kg^{-1} in patients with suspected or confirmed aspergillosis. A switch to liposomal amphotericin was performed in patients whose creatinine levels doubled during the treatment, or when the baseline creatinine was higher than 1.4 mg dl^{-1}. The primary outcome of this study was nephrotoxicity, which was also defined as the occurrence of twofold increase in baseline creatinine. Mortality within 14 days, absence of fungal breakthrough infections during treatment and the resolution of proven fungal infections were also analysed as secondary outcomes. A total of 77 patients were included for analysis. The mean increase in creatinine, the mean peak fraction of creatinine during treatment and the reduction of creatinine clearance were significantly lower in patients treated with a continuous 24-h infusion of amphotericin B deoxycholate. Renal impairment occurred significantly less frequently with continuous infusion of amphotericin B deoxycholate compared with 4 h infusion of amphotericin B [10% vs. 45%, respectively, odds ratio (OR) 0.14; 95% confidence interval (CI) 0.04–0.5, $P < 0.001$]. The authors identified a target infusion rates associated with less nephrotoxicity <0.08 mg kg^{-1} h^{-1}. The analysis of the subgroups of patients who were submitted to bone marrow transplants and of those who used nephrotoxic drugs concurrently showed a reduction in renal toxicity with continuous infusion, maintaining the statistical significance seen in the overall analysis. Mortality was significantly different in the two groups (14-day survival: 95% in continuous infusion vs. 79% in 4-h infusion, $P = 0.03$), and it was not directly related to fungal infection. There was no difference in the breakthrough fungaemia between the two groups.

A counterpoint to the evidence of the benefit of continuous amphotericin B deoxycholate infusion was a study performed by Altmannsberger *et al.* [26] The authors describe the experience with amphotericin B deoxycholate by retrospectively analysing two cohorts of patients, one with a 6-h infusion and the other with a continuous 24-h infusion. No differences were observed in relation to nephrotoxicity among the groups. The 4-week mortality was also similar among the two treatment arms. In this study, it was concluded that although it is feasible to administer amphotericin B deoxycholate in a continuous infusion, it did not present advantages or benefits compared with conventional 6-h infusion, suggesting that this benefit would be achieved only using the lipid formulations of amphotericin B. The study was funded by the pharmaceutical industry, which developed *Ambisome* (liposomal formulation of amphotericin B.)

Schulenburg *et al.* [27] published a report on an open, prospective study of 17 patients with febrile neutropenia and haematological malignancies. Amphotericin B deoxycholate was used in a continuous infusion and the data were compared with a control group consisting of 10 patients. The continuous infusion of amphotericin B deoxycholate resulted in no acute infusional reactions, hypokalaemia, and severe nephrotoxicity than controls treated 2–6 h infusions. There was no difference in the analysis of efficacy (mortality and resolution of the fever). Once again, it was concluded that the continuous infusion of amphotericin B deoxycholate is safe, practicable and effective in this patient population.

A recent prospective study included patients with disseminated cryptococcosis and AIDS who received continuous 24-h infusion of amphotericin B deoxycholate (0.7 mg kg^{-1} daily) and oral 5′-flucytosine (25 mg kg^{-1} four times a day) during an induction phase of 14 days.[28] We measured fungicidal activity using serial quantitative cultures of cerebrospinal fluid (CSF) obtained from lumbar punctures on days 3, 7 and 14 of treatment. At this time, six patients have been included in the study. The analysis has shown that all six patients included presented a progressive reduction in CSF cryptococcal colony-forming units (CFU) and CSF was sterile at 2 weeks of treatment. Although two patients developed severe hypokalaemia, glomerular renal function was well preserved in all patients with creatinine serum levels below 1.5 mg dl^{-1} at the end of 14 days of antifungal therapy. The authors observed the occurrence of anaemia (decrease in haemoglobin at least of 3 g dl^{-1}) in three patients.

Considering possible interactions with other medications, which might compromise its stability, continuous infusion of amphotericin B deoxycholate should be carried out through a specific and unique central venous line.

Conclusions

The data so far reviewed suggest that the use of amphotericin B deoxycholate in a continuous 24-h infusion seems to be safe and effective in the context of haematological malignancy, haematopoietic stem cell transplant with febrile neutropenia and HIV-infected patients with cryptococcosis. In general, the retrospective and prospective studies and the results of the clinical trials available suggest a clinical and microbiological effectiveness similar to the standard of treatment with amphotericin B deoxycholate. The nephrotoxicity benefit achieved is clear and comparable with that reported with the use of

lipid formulations of amphotericin B. However, a large number of patients enrolled in the studies did not present a proof of fungal infection, because of the inherent difficulty in diagnosing these conditions. Furthermore, treatment efficacy may vary with different aetiologies, and further investigations are necessary to evaluate the clinical and microbiological response against the different fungal pathogens.

The low cost associated with this type of treatment makes this strategy an important alternative, especially at centres with limited resources, and one may obtain the advantages of toxicity reduction characteristics of lipid formulations much more economically. However, the studies published so far included a too small number of patients to evaluate the effectiveness. Further prospective randomised studies are needed, especially in patients with proven fungal infection, for the large-scale adoption of this innovative mode of treatment in the routine use of amphotericin B deoxycholate.

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