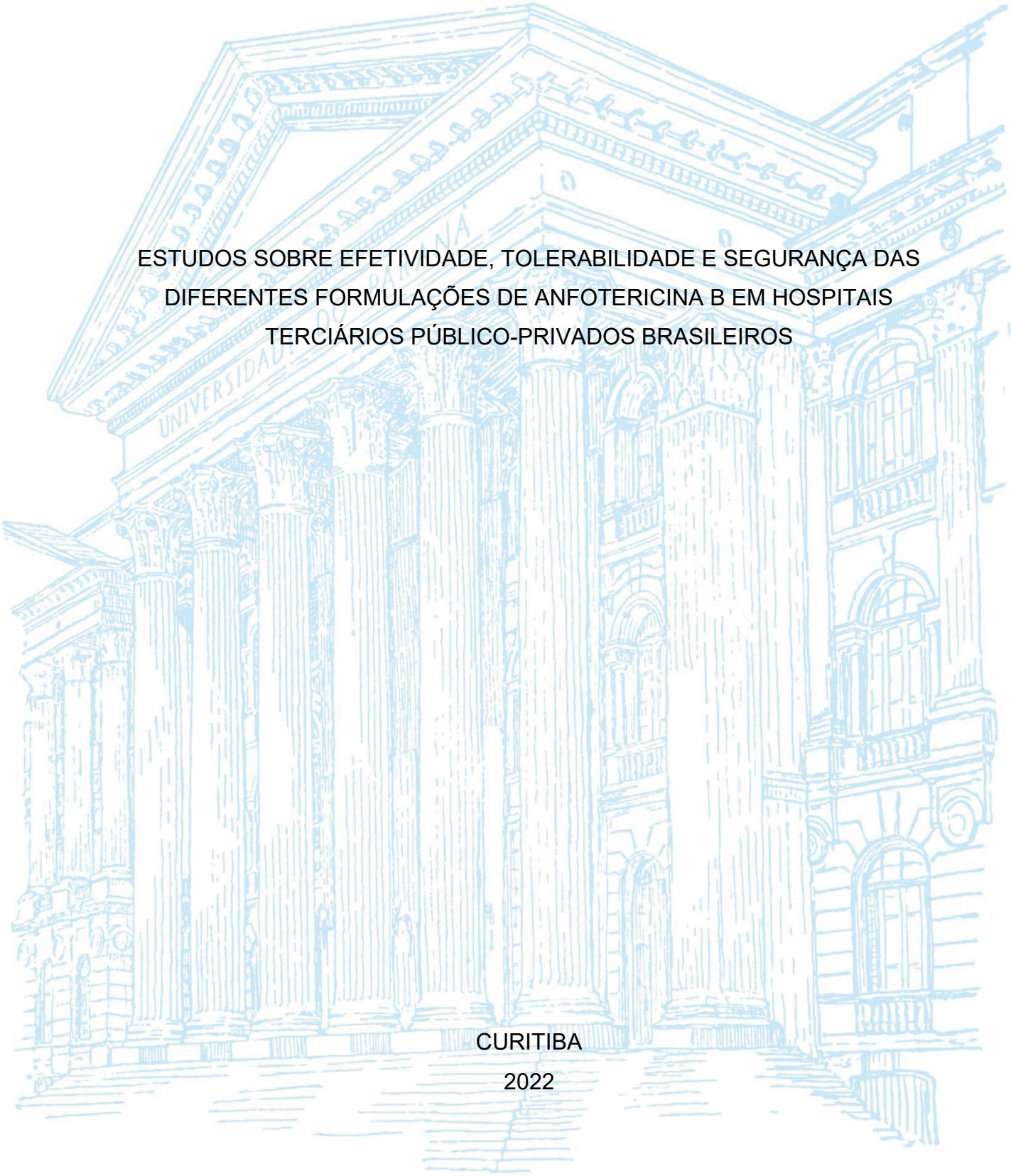
UNIVERSIDADE FEDERAL DO PARANÁ

FRANCELISE BRIDI CAVASSIN



ESTUDOS SOBRE EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS TERCIÁRIOS PÚBLICO-PRIVADOS BRASILEIROS

CURITIBA

2022

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Tese apresentada ao curso de Pós-Graduação em Medicina Interna e Ciências da Saúde, Setor de Ciências da Saúde, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Doutor em Medicina Interna e Ciências da Saúde.

Orientador: Prof. Dr. Flávio de Queiroz Telles Filho

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TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação MEDICINA INTERNA E CIÊNCIAS DA SAÚDE da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **FRANCELISE BRIDI CAVASSIN** intitulada: **"ESTUDOS SOBRE EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS TERCIÁRIOS PÚBLICO-PRIVADOS BRASILEIROS."**, sob orientação do Prof. Dr. FLÁVIO DE QUEIROZ TELLES FILHO, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de doutora está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

Curitiba, 01 de Dezembro de 2022.

Assinatura Eletrônica
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Presidente da Banca Examinadora

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Aprendemos a voar admirando os que já alçaram voos antes de nós.

Dedico este trabalho ao melhor mestre, micologista e pesquisador que conheci nesses últimos quatro anos de minha jornada,

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RESUMO

Introduzidos no final da década de 1950, os polienos representam a família mais antiga de drogas antifúngicas. A descoberta da anfotericina B e seus usos terapêuticos é considerada um dos marcos científicos mais importantes do século XX. Apesar de seu potencial tóxico, permanece útil no tratamento de doenças fúngicas invasivas devido ao seu amplo espectro de atividade, baixo índice de resistência e excelente ação clínica e farmacológica. A toxicidade bem relatada e definida da droga convencional fez com que muita atenção fosse dada ao desenvolvimento de novos produtos que pudessem minimizar esse efeito. Como resultado, surgiram formulações de base lipídica da anfotericina B e, mesmo mantendo o princípio ativo em comum, apresentam características distintas que podem influenciar os resultados terapêuticos. Este estudo apresenta uma visão geral das propriedades farmacológicas das diferentes formulações para uso sistêmico de anfotericina B disponíveis para o tratamento de infecções fúngicas invasivas, destacando as características relacionadas a suas estruturas químicas, farmacocinéticas, interações fármaco-alvo, estabilidade, entre outras, e apontar os aspectos mais relevantes para a prática clínica.

Palavras-chave: Efetividade. Pesquisa comparativa da efetividade. Tolerabilidade medicamentosa. Anfotericina B. Segurança do paciente.

ABSTRACT

Introduced in the late 1950s, polyenes represent the oldest family of antifungal drugs. The discovery of amphotericin B and its therapeutic uses is considered one of the most important scientific milestones of the twentieth century. Despite its toxic potential, it remains useful in the treatment of invasive fungal diseases owing to its broad spectrum of activity, low resistance rate, and excellent clinical and pharmacological action. The well-reported and defined toxicity of the conventional drug has meant that much attention has been paid to the development of new products that could minimize this effect. As a result, lipid-based formulations of amphotericin B have emerged and, even keeping the active principle in common, present distinct characteristics that may influence therapeutic results. This study presents an overview of the pharmacological properties of the different formulations for systemic use of amphotericin B available for the treatment of invasive fungal infections, highlighting the characteristics related to their chemical, pharmacokinetic structures, drug-target interactions, stability, and others, and point out the most relevant aspects for clinical practice.

Keywords: Effectiveness. Comparative research. Drug tolerability. Amphotericin B. Patient safety.

SUMÁRIO

1 INTRODUÇÃO

As infecções fúngicas invasivas (IFIs) têm uma incidência inferior às infecções superficiais, porém são mais preocupantes porque estão associadas a taxas de mortalidade inaceitavelmente elevadas (BROWN et al., 2012). São difíceis de detectar e tratar e podem ser associadas à morbidade e mortalidade substanciais e essas questões estão se tornando cada vez mais evidentes (BENEDICT et al., 2017).

Nas últimas décadas têm-se observado um aumento da carga global das doenças fúngicas, dada a expansão do número de pacientes em risco para essas infecções, incluindo os que convivem com o vírus da imunodeficiência humana (HIV), os transplantados, pacientes com câncer, os que recebem imunomoduladores, os recém-nascidos prematuros e os idosos. Viagens e mudanças no clima também podem resultar em mudanças na distribuição geográfica dos fungos (VALLABHANENI et al, 2016). A carga e o impacto médico das doenças fúngicas são amplamente desconhecidos e frequentemente subestimados, especialmente para infecções fúngicas endêmicas (QUEIROZ-TELLES et al, 2017).

Pacientes com IFIs graves são normalmente diagnosticados em hospitais público-privados terciários e podem representar um desafio terapêutico para o sistema de saúde em países em desenvolvimento. Estima-se que, no mundo, mais de um bilhão de pessoas sofrem de alguma infecção fúngica (GAFFI.ORG, 2018) e mais de 1,5 milhão de pessoas morrem a cada ano, sendo que um dos quatro gêneros *Cryptococcus*, *Candida*, *Aspergillus* ou *Pneumocystis* é relatado como causador em mais de 90% das mortes relacionadas a fungos (CORNELY et al, 2017).

No Brasil, poucas doenças fúngicas são notificadas ao Ministério da Saúde (MS) como coccidioidomicose, histoplasmose e paracoccidioidomicose. Em 2011, dados do Departamento de Informática do Sistema Único de Saúde (DATASUS) apontou que a incidência (/1000) de hospitalizações por coccidioidomicose foi de 7,12; para histoplasmose, 2,19; e para paracoccidioidomicose, 7,99. No entanto, a carga de outras doenças fúngicas prevalentes no país (cromoblastomicose, mucormicose e esporotricose) é, ainda, desconhecida (DATASUS.GOV.BR, 2018).

Nas duas últimas décadas houve um aumento no número de medicamentos antifúngicos disponibilizados para o tratamento de IFIs. Dentre eles, os chamados polienos podem ser divididos em convencionais – que incluem nistatina e anfotericina B desoxicolato (D-AMB) e formulações baseadas em lipídios de anfotericina B

(LFABs) – desenvolvidas na tentativa de preservar a função renal e minimizar demais eventos adversos e toxicidade.

Estudos pioneiros que avaliaram LFABs de uso sistêmico – lipossomal (L-AMB) e complexo lipídico (ABLC) mostraram redução na frequência da toxicidade renal ao serem comparadas à D-AMB (WALSH et al., 1998; WALSH et al., 1999). Porém, um estudo comparativo dessas formulações realizado em 2010 não garantiu vantagens de uma formulação lipídica em relação à outra (SAFDAR, 2010) além de carecer dados na literatura que demonstrem suas semelhanças, diferenças, vantagens e desvantagens, com base em estudos mais atuais (FALCI e PASQUALOTTO, 2015).

Pacientes admitidos em hospitais públicos brasileiros, com diagnóstico de IFI comprovada, têm acesso gratuito ao ABLC fornecido pelo MS. No Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR), mais de 100 intervenções farmacológicas com tal formulação foram administradas a pacientes durante os últimos anos. Este número é significativamente maior se forem considerados todos os tratamentos – não somente o complexo lipídico. Apesar do uso frequente, faltam dados que avaliem importantes desfechos clínicos em relação à essa formulação em específico empregada.

1.1 JUSTIFICATIVA

Tendo em vista a relevância do tema exposto, justificou-se o presente estudo multicêntrico pelo robusto banco de dados gerado, e que foi capaz de fornecer novas e atualizadas evidências sobre a efetividade, a tolerabilidade e a segurança das diferentes formulações de anfotericina B de uso sistêmico disponíveis para uso no Brasil.

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1.2 OBJETIVOS

1.2.1 Objetivo geral

Avaliar a efetividade, tolerabilidade e segurança das diferentes formulações de anfotericina B de uso sistêmico disponíveis em hospitais público-privados terciários brasileiros.

1.2.2 Objetivos específicos

1. Revisar as propriedades farmacológicas das diferentes formulações de anfotericina B disponíveis para uso, destacando suas estruturas químicas, farmacocinéticas, interações droga-alvo, estabilidade, entre outras características, e os aspectos mais relevantes para a prática clínica;
2. Coletar dados clínico-epidemiológicos a partir de prontuários de pacientes que fizeram uso das formulações de anfotericina B em um período de seis anos;
3. Estimar a incidência dos pacientes internados comprovadamente diagnosticados com infecção fúngica e tratados com anfotericina B no período de seis anos; a etiologia dessas infecções; e o índice de sobrevivência destes pacientes;
4. Analisar o banco de dados obtido nos diversos hospitais terciários brasileiros em relação à efetividade, tolerabilidade e segurança das diferentes formulações de anfotericina B.

1.3 METODOLOGIA

1.3.1 Tipo de pesquisa e definição dos participantes

Este é um estudo multicêntrico, de natureza observacional (coorte histórica) conduzido em dez hospitais público-privados terciários brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR).

Além do centro coordenador, os demais hospitais participantes e coparticipantes foram definidos após duas reuniões realizadas nos meses de maio e novembro de 2018 em Brasília-DF e que contaram com a participação de representantes do Grupo Técnico de Micoses Sistêmicas da Secretaria de Vigilância em Saúde (SVS) do Ministério da Saúde do Brasil. Os centros são Hospital Pequeno Príncipe (HPP/PR), Hospital Erasto Gaertner (HEG/PR), Hospital Universitário do Oeste do Paraná (HUOP/PR), Hospital de Clínicas de Porto Alegre (HCPA/RS),

Instituto de Infectologia Emílio Ribas (IIER/SP), Universidade Federal de São Paulo (UNIFESP/SP), Hospital de Clínicas de São Paulo (HCFMUSP/SP), Hospital de Doenças Tropicais Dr. Anuar Auad (HDT/HAA/GO) e Hospital São Rafael (HSR/BA).

1.3.2 Critérios de inclusão e exclusão

Foram incluídos na coorte histórica, prontuários de pacientes que preencheram os seguintes critérios:

a) Pacientes que estiveram internados em algum dos dez hospitais público-privados terciários participantes no período de seis anos (2014 – 2019);

c) Suspeitados ou diagnosticados com algum tipo de infecção fúngica invasiva no mesmo período;

d) Tratados com pelo menos duas doses de uma das formulações de uso sistêmico de anfotericina B: desoxicolato (D-AMB), lipossomal (L-AMB) ou complexo lipídico (ABLC).

Não houve restrição quanto a idade, sexo ou doença de base.

Foram excluídos prontuários de pacientes com exposição prévia à anfotericina B e àqueles em que consta somente a prescrição de uma única dose do antifúngico no período determinado.

1.3.3 Coleta de Dados

Os dados foram obtidos exclusivamente de prontuários de pacientes que estiveram internados nos hospitais participantes e coparticipantes previamente definidos no período de 2014 a 2019. Um instrumento de pesquisa foi criteriosamente elaborado (ANEXO 1) e disponibilizado para cada centro participante/coparticipante. Ao final, cada centro foi responsável por reportar seus achados para um formulário eletrônico padronizado desenvolvido via plataforma *Research Electronic Data Capture* (REDCap) disponível em https://siga.ufpr.br/redcap/surveys/?s=TMXY78MC3T (HARRIS et. al 2009; HARRIS et. al 2019).

Para que todos os dez centros estivessem igualmente aptos a iniciarem suas coletas foi disponibilizado para os pesquisadores e seus auxiliares um dicionário de termos para consulta (ANEXO 2), expondo exatamente como cada campo do instrumento de pesquisa devesse ser coletado. Além disso, treinamentos *in situ* e/ou *online* foram realizados individualmente e durante todo o processo, além de suporte remoto fornecido sempre que solicitado.

Coube ao centro coordenador (CHC/UFPR) avaliar todos os elementos em relação à consistência das informações. Dados inconsistentes foram reenviados aos centros de origem para esclarecimentos ou correções.

1.3.4 Aspectos éticos

A pesquisa foi submetida ao Comitê de Ética e Pesquisa do Complexo Hospital de Clínicas da Universidade Federal do Paraná (UFPR) em 14 de abril de 2018 sob o nº CAAE: 87619218.5.0000.0096 e aprovado em 26 de junho de 2018 sob o parecer nº 2.735.720. Todos os demais centros participantes ou coparticipantes também tiverem seus parecerem aprovados conforme ANEXO 3.

2 REVISÃO DE LITERATURA

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Highest percentile 72% = Novo Qualis CAPES A3.

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Sumário

ARTIGO 1

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REVIEW

Sixty years of Amphotericin B: An Overview of the Main Antifungal Agent Used to Treat Invasive Fungal Infections

Francelise B. Cavassin · João Luiz Baú-Carneiro · Rogério R. Vilas-Boas · Flávio Queiroz-Telles

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ABSTRACT

Introduced in the late 1950s, polyenes represent the oldest family of antifungal drugs. The discovery of amphotericin B and its therapeutic uses is considered one of the most important scientific milestones of the twentieth century . Despite its toxic potential, it remains useful in the treatment of invasive fungal diseases owing to its broad spectrum of activity, low resistance rate, and excellent clinical and pharmacological action. The well-reported and defined toxicity of the conventional drug has meant that much attention has been paid to the development of new products that could minimize this effect. As a result, lipid-based formulations of amphotericin B have emerged and, even keeping the active principle in common, present distinct characteristics that may influence therapeutic results. This study presents an overview of the pharmacological properties of the different formulations for systemic use of amphotericin B available for the treatment of invasive fungal infections, highlighting the characteristics related to their chemical, pharmacokinetic structures, drug–target interactions, stability, and others, and points out the most relevant aspects for clinical practice.

Keywords: Fungal disease; Lipid formulation; Polyenes; Safety; Tolerability

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Key Summary Points

Amphotericin B (AMB) is still considered one of the most important antifungals of the last 60 years.

We present an overview of the pharmacological properties of the different formulations for systemic use of AMB available for the treatment of invasive fungal infections.

The study highlights its chemical characteristics, pharmacokinetic, structures, drug–target interactions, stability, bioequivalence, and others, and points out the most relevant aspects for clinical practice.

The indications for the different formulations of AMB are based on the latest consensus and guidelines, and studies on their toxicity are based on the main clinical trials conducted in humans.

A timeline presents the main scientific milestones for AMB over the decades.

An updated list of the last 2 years of clinical trials that seek to improve the use of AMB in different situations is also provided.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13325681.

INTRODUCTION

Licensed in 1959 [1], amphotericin B (AMB) was initially designed for the treatment of local mycotic infections and later approved for the treatment of progressive and potentially fatal fungal infections [2]. After 60 years, it is still an important option in the treatment of fungal diseases.

Traditionally, the drug is administered as a formulation of deoxycholate amphotericin B (D-AMB) capable of forming micelles in aqueous solution [3]. Besides being a long-known medication, AMB has important side effects, such as nephrotoxicity, which have limited its indiscriminate use [4–6]. Most of the time, patients who need intervention with D-AMB are severely compromised because of their underlying diseases and comorbidities, and therefore, they end up becoming vulnerable to the reported toxic effects, especially when combined with other drugs.

To overcome this impasse, new systemic therapeutic options have been proposed: amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AMB). There was a third lipid formulation known as AMB colloidal dispersion (ABCD), presented as uniform disk-shaped particles, that was discontinued in 2011 because of its high rate of infusion-related events and it is no longer manufactured [7, 8]. Although ABLC and L-AMB have the same active principle in common, their pharmacological characteristics distinguish them and may influence the final therapeutic results. Their chemical structures, pharmacokinetics, drug–target interactions, stability, bio and therapeutic equivalences share similarities but also present peculiarities, notably when compared to the conventional formulation.

This study presents an overview of the pharmacological and biopharmaceutical properties of the different systemic formulations of AMB available for the treatment of invasive fungal infections and highlights the most relevant aspects in 60 years for clinical practice. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

WHY THE GOLD STANDARD?

Amphotericin B is a life-saving drug in the treatment of serious systemic fungal infections

and is still the most widely used antifungal in and intensive care, despite the development of a series of new antifungal agents, especially the second-generation triazoles and the echinocandins.

These 60 years of clinical experience have proven that AMB is a reliable antifungal agent. At the time of its introduction and for decades, doctors had few other therapeutic options, and they learned and adapted to use it in order to minimize its toxicities.

The new therapeutic options also offer great prospects for treatment. Such options include improved azole antifungal agents, the echinocandin class, in addition to constant studies in search of new lipid formulations of AMB itself. However, it has been in recent years that these agents have proven their worth in a variety of clinical settings, providing high rates of effectiveness with minimal safety-related problems. Therefore, over time, it is natural that the use of conventional AMBs and even lipid formulations of amphotericin B (LFABs) may have limited use, as the evidence with the new agents, with new combination schemes, will show improvements in patient care and its benefits will be increasingly noticed.

Despite these advances, AMB remains in use both in medical practice and in clinical trials owing to the wide possibility of licensed indications. In addition, AMB remains the treatment of choice for many serious fungal infections in vulnerable hosts owing to its excellent spectrum of activity and its low resistance rates. To date, it continues to be the agent with the widest spectrum of action and the lowest resistance potential of any known antifungal agent [9].

Some characteristics that maintain its status as the gold standard are the low cost of conventional AMB therapy, the high acceptance of this formulation in continuous use by neonates, the improvement of toxicity rates with the arrival of the LFABs, and its intrathecal use in *Coccidioides immitis* meningitis [10, 11]. It is also noteworthy that there are individuals who actually tolerate conventional therapy better than advanced formulations [12]. Basically, these are the fundamentals that make the medical community consider the use of AMB as a therapeutic standard in addition to a standard comparator for clinical trials among antifungal agents.

With the new pharmaceutical forms and formulations, such as the possibility of the long-awaited AMB for oral use and the production of a generic version, for example, the cost of LFABs may start to decrease and its wide access will be offset by reduced rates of toxicity.

Finally, the newest treatment guidelines still mention its use as first-line therapy in certain defined situations, which reinforces AMB as the official holder of the gold standard title in the treatment of serious invasive fungal diseases.

HISTORICAL FINDINGS, CHARACTERISTICS, AND STRUCTURES

Amphotericin B belongs to the class of polyene macrolides which also comprises amphotericin A and nystatin, the latter being considered the first antifungal agent developed for the treatment of mycoses [13], despite its production as a systemic agent being avoided because of serious toxicities.

The drug was discovered in 1956 by Donovick, Gold, Pagano, and Stout [14] following the fermentation of the actinomycete *Streptomyces nodosus*, originally identified as M-4575, isolated from a soil sample collected in the Orinoco River region, in Venezuela. As a therapeutic agent, it was licensed in 1959, on the basis of available and non-comparative data [1], and became accessible commercially in 1960 as Fungizone® (Bristol-Myers-Squibb, USA), a colloidal suspension of AMB.

Currently AMB is certified for the treatment of various fungal and potentially fatal infections such as opportunistic mycoses, e.g., aspergillosis, candidiasis, cryptococcosis, fusariosis, mucormycosis, hyalohyphomycosis, and phaohyphomycosis, as well as severe and widespread forms of endemic mycoses, e.g., histoplasmosis, paracoccidioidomycosis, blastomycosis, coccidioidomycosis, sporotrichosis, talaromycosis (*Talaromyces marneffei*, formally *Penicillium marneffei*), and emergomycosis [15–19]. Lipotrophic molecules such as deoxycholate,

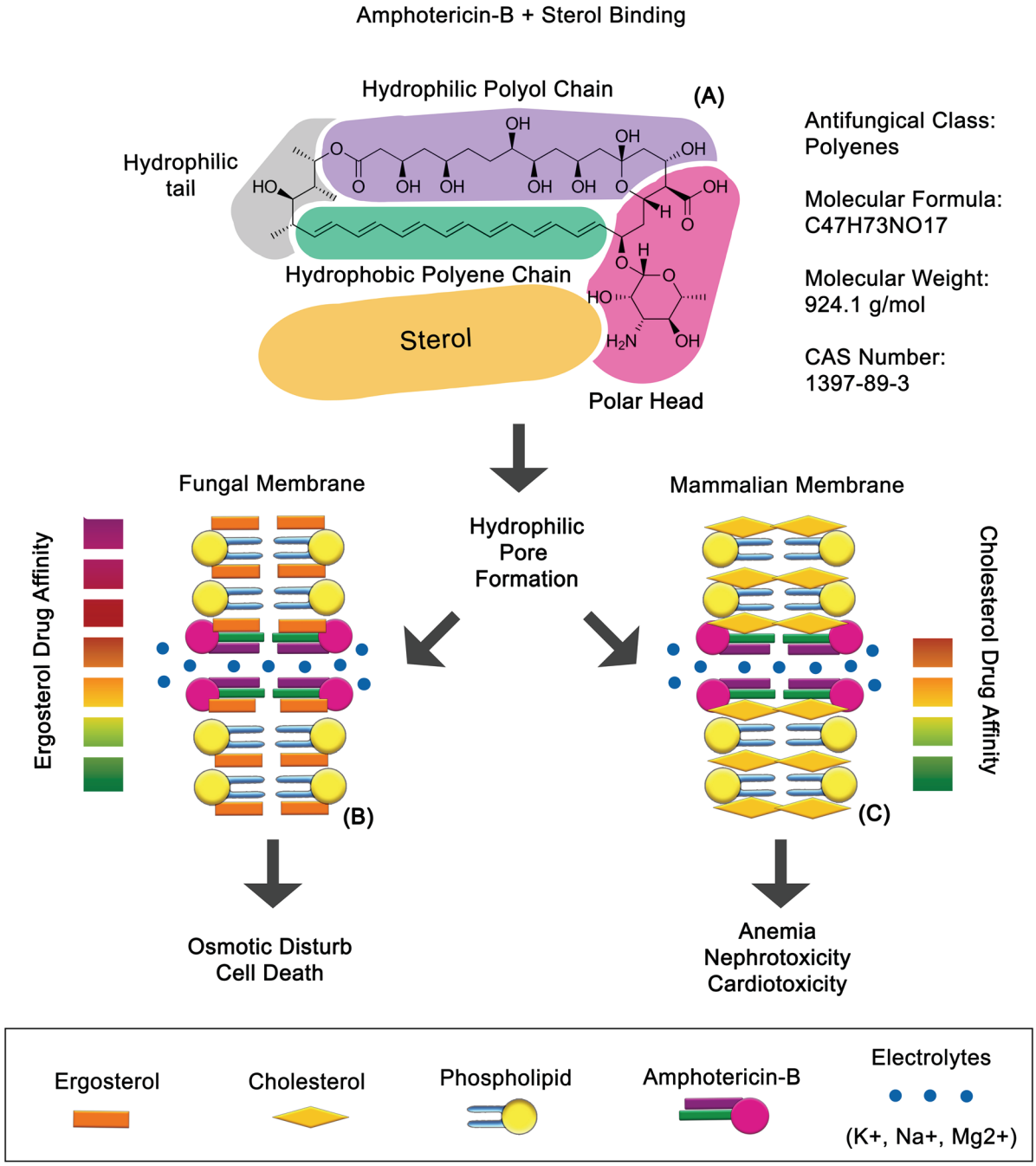

Fig. 1 **a** Drug summary and 2D chemical structure of AMB and its binding to the cell's sterol component; **b** AMB mechanism of action in a fungal cell; **c** AMB mechanism of toxicity in a mammalian cell

liposomes, and lipid complexes were added in the intravenous formulations for systemic use because of the insolubility of the standard form.

AMB comprises a 38-membered macrocyclic ring formed by lactonization and it has a chain of unsubstituted conjugated double bonds (heptaene) (Fig. 1a). On the opposite side, a polyhydroxylated chain with seven free hydroxyl groups guarantees it an amphipathic characteristic. A mycosamine residue (lactone) rests

at one end of the molecule, with a free amino group, forming a side chain [20]. The conventional formulation contains approximately 41 mg of sodium deoxycholate and 20.2 mg of phosphate buffer [21]. Sodium deoxycholate increases the solubility of amphotericin B in water, because, although AMB has an amphiphilic region, its solubility in water is low. Sodium deoxycholate also stabilizes the micellar suspension formed [22, 23]. The hydrophobic part of the molecule binds to ergosterol, the main sterol in the cytoplasmic membrane of fungi. As a result of this connection, pores and channels are formed in the plasma membrane that allow the extravasation of electrolytes from the intracellular medium such as potassium, ammonium, and phosphate in addition to carbohydrates and proteins, thus causing cell death [24–28].

This mechanism of action (Fig. 1b), added to an induction of oxidative damage in the fungal cell [28], guarantees its fungicidal characteristic. Nevertheless, the success of this interaction depends on the concentration of the drug in body fluids and on the fungal specimen's susceptibility to it.

Besides its affinity for the fungal ergosterol, AMB also stands out as a molecule with affinity for cholesterol present in mammalian cells (Fig. 1c). This characteristic per se explains why kidneys, heart, and blood cells are damaged during some therapeutic schemes [25, 29]. Despite that, there is no other antifungal medication that combines so many positive characteristics. Its potent fungicidal activity, broad spectrum of action, and rare induction of resistance guarantees it as an extremely effective option among other chemotherapeutic possibilities [30]. Studies have been conducted to improve lipid preparations as vehicles for new formulations such as liposomes [31–37], lipid complexes [38–40], emulsions [41–46], nanoparticles with dimercaptosuccinic acid [47], cationic lipid–polymer hybrids targeting macrophages [48], and Pluronic F127 micelles [49]. Figure 2 illustrates the main historical events of the last 60 years, maintaining AMB as the gold standard for the treatment of most invasive fungal infections (IFIs).

The current lipid formulations of amphotericin B (LFABs) available for clinical use differ in pharmacological characteristics such as structure, shape, size, composition, and toxicity—when compared to the conventional formulation (Table 1). ABLC and L-AMB allow the administration of higher doses and vary in efficacy and toxicity depending on the preparation and the species of fungus. Both benefits were goals for the development of LFABs, and the approval of these formulations was based on their comparison with conventional amphotericin B in clinical trials that are also cited in Table 1 for any further reading.

Although licensing decisions in the USA for LFABs have been based primarily on data from open non-comparative studies, there is now more available data that supports the effectiveness and safety of these compounds in the treatment of systemic fungal infections. The use of higher concentrations of AMB in less toxic lipid formulations is of great importance owing to its high clinical tolerability. However, undesirable effects such as fever, chills, stiffness, drowsiness, slight elevation in liver function tests, renal dysfunction, and cardiopulmonary toxicity have been documented even in patients who received those liposomal subtypes [58]; therefore, studies are still being carried out to find ways to reduce these events further. Recent research presented results regarding the development of nanoparticles, signaling superiority of these compounds to the conventional preparations [46–48, 60].

Infusion-related toxicity is a side effect which was initially attributed to the conventional formulation, as a result of the pro-inflammatory response to cytokines that manifests during the first minutes of administration. The symptoms are well controlled with antihistamines, analgesics, and corticosteroids [106].

It was the study by Gigliotti et al. [107] that postulated the chills and fever produced by an infusion of AMB were mediated through prostaglandin E_2 synthesis. After this understanding new findings started bringing attention to the use of premedication as new way to better prevent these side effects. Some trials—even decades before that—revealed that hydrocortisone could be effective in the prevention of infusion-related reactions because of its

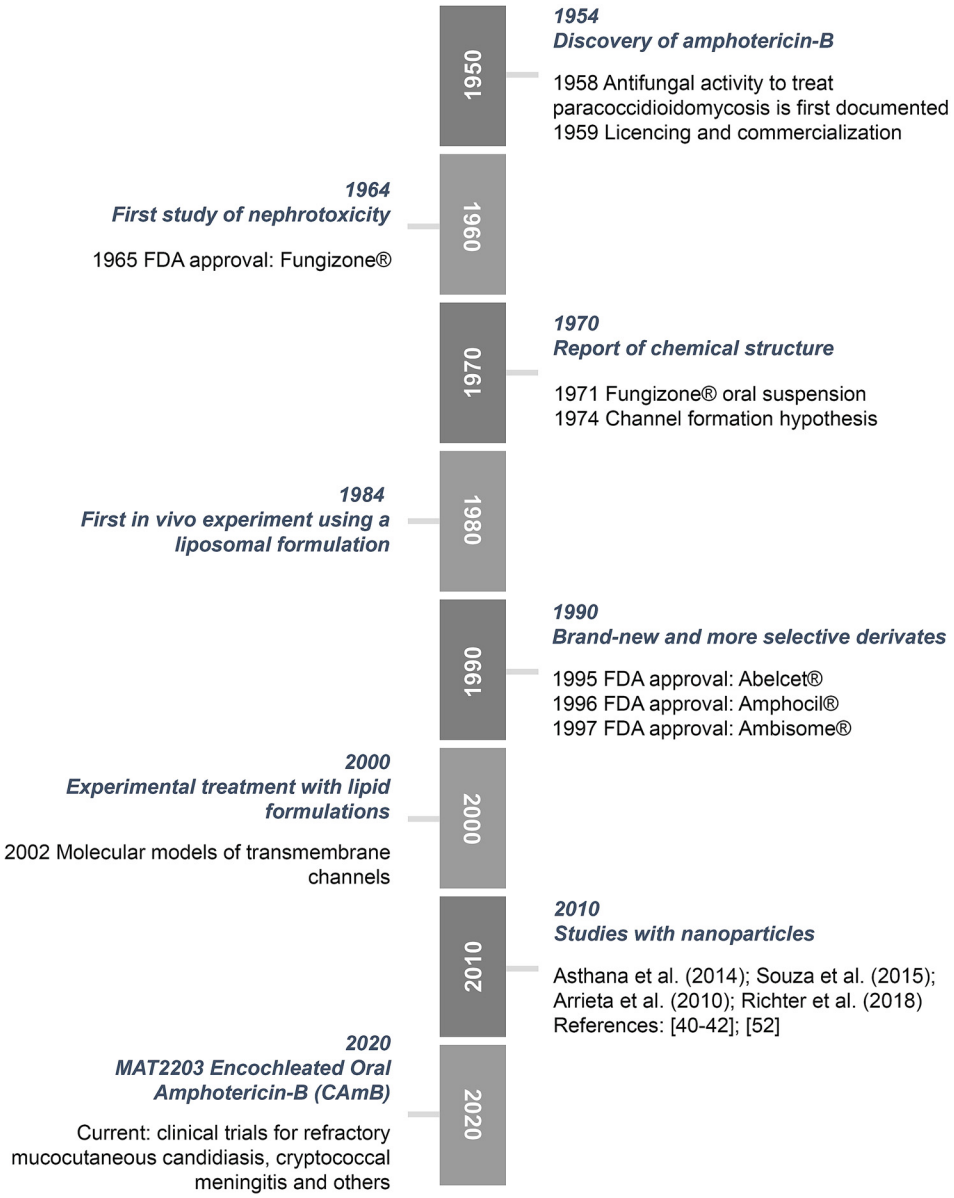

Fig. 2 Amphotericin B over the decades

cytokine transcription inhibitory property [108]. There are also studies about the use of opioids (mainly represented by meperidine IV in bolus) as a good option in ameliorating the infusion reactions. Authors argue that meperidine can eliminate these reactions more effectively and more rapidly than simply discontinuing the AMB [109]. Acetaminophen and metamizole are also commonly reported as drugs used for premedication.

In short, reactions related to the infusion of conventional therapy are possibly treatable. For patients who develop undesirable reactions, switching to an LFAB can also be a solution.

However, in 2003, Roden et al. [110] stated that the infusion of L-AMB could result in an idiosyncratic reaction manifested as a triad of chest pain and/or discomfort, flank and/or abdominal pain and dyspnea. This reaction is credited more to the liposome than the active drug itself [111], although Wade et at. [112]

Table 1 Pharmacological characteristics of and other general information on lipid-based formulations of amphotericin B (LFABs) available for systemic use and conventional formulation

Formulation	LFABs		Conventional
	ABLC	L-AMB	D-AMB
Reference	Abelcet®	AmBisome®	Fungizone®
Pharmaceutical industry	The Liposome Company Inc., NJ	Fujisawa Healthcare Inc., IL	Apothecon Products, Princeton Inc., NJ
FDA approval	1995	1997	1965
Structure	Multilamellar ribbon-shaped complex	Small spherical unilamellar liposomes	Micellar structure
Design	Fig. 3	Fig. 4	Fig. 5
Size (nm)	1600–11,000	< 100	< 25
Composition	AMB suspension complex with DMPC and DMPG	AMB encapsulated in liposomes consisting of hydrogenated soy phosphatidylcholine, cholesterol, and DMPG	Colloidal dispersion of AMB with deoxycholate salt in aqueous glucose solution
AMB content	100 mg in 20 mL of isotonic suspension	50 mg lyophilized powder	50 mg lyophilized powder
Standard dosage (mg/kg)	1.0–5.0	3.0–5.0	0.25–1.0
LD50 (mg/kg)	40	175	2
Distribution	Spleen ≫ liver = lung > kidney	Spleen ≫ liver > lung = kidney	Liver > spleen > lung > kidney
BBB overpass [50]	Partial	Yes	Yes
Indications* (Grade A or B of evidence) [15–17, 19, 51]	Yeast fungi: *Pseudozyma* spp., *Trichosporon* spp., *Candida* spp. Filamentous fungi: *Fusarium* spp., black fungi/ phaeohyphomycetes/ dematiaceous fungi Endemic infections: coccidioidomycosis, emergomycosis, paracoccidioidomycosis Invasive fungal infections in patient's refractory or intolerant to conventional therapy (D-AMB) or when L-AMB is not available	Yeast fungi: *Geotrichum* spp., *Kodamaea* spp., *Malassezia* spp., *Pseudozyma* spp., *Rhodotorula* spp., *Saccharomyces* spp., *Saprochaete* spp., *Sporobolomyces* spp., *Trichosporon* spp., *Candida* spp. Filamentous fungi: *Fusarium* spp., phaeohyphomycetes/dematiaceous fungi/black fungi, *Schizophyllum* and other basidiomycetes, *Scopulariopsis* spp., *Penicillium* spp., Paecilomyces Endemic infections: blastomycosis, coccidioidomycosis, emergomycosis, histoplasmosis, sporotrichosis, talaromycosis (penicilliosis) Empirical therapy for suspected fungal infection in patients with febrile neutropenia	Yeast fungi: *Geotrichum* spp., *Kodamaea ohmeri*, *Malassezia* spp., *Rhodotorula* spp., *Saccharomyces* spp.,*Trichosporon* spp., *Candida* spp. Filamentous fungi: – Endemic infections: blastomycosis, coccidioidomycosis, emergomycosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, talaromycosis (penicilliosis)

Table 1 continued

Formulation	LFABs		Conventional
	ABLC	L-AMB	D-AMB
Main studies** about therapeutical efficacy on IFI	[52–59]	[57, 60–71]	[62, 72–77]
Main studies** about toxicity	Renal	[53, 56, 57, 78–81]	
	Cardiac***	[82–93]	
	Hematological	[55, 78, 94]	
	Infusion-related	[53, 55, 57, 95–98]	
Comparative studies between different AMB formulations		[24, 79, 98–105]	

LFABs lipid-based formulations of amphotericin B, *ABLC* amphotericin B lipid complex, *L-AMB* liposomal amphotericin B, *D-AMB* amphotericin B deoxycholate, *DMPC* dimyristoylphosphatidylcholine, *DMPG* dimyristoylphosphatidylglycerol, *AMB* amphotericin B, *IFI* invasive fungal infection, *FDA* Food and Drug Administration, *BBB* blood–brain barrier, *LD50* median lethal dose

*Based on the most recent consensus

**Human clinical trials only

***Case reports described in the literature

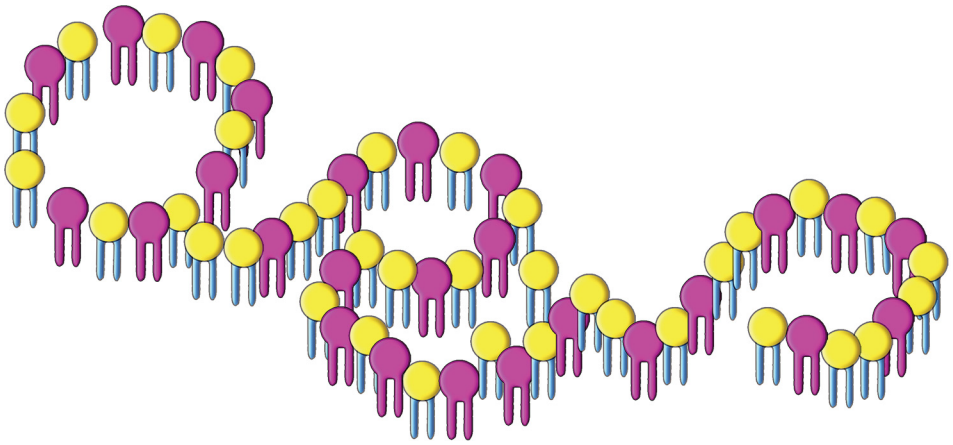

Fig. 3 Amphotericin B lipid complex (ABLC). Amphotericin B Phospholipid

ensured that the toxicity related to the infusion of L-AMB is consistently less that other formulations of polyenes, including ABLC.

For the lipid complex of AMB there are recommendation in case of adverse events, including the infusion-related ones. The document suggests as optimal premedication the use of hydrocortisone and chlorphenamine (antihistamine agent) given 15–30 min before the infusion. Other advice includes the minimum infusion time of 2 h and adequate hydration before and after dosing for renal function improvement [113].

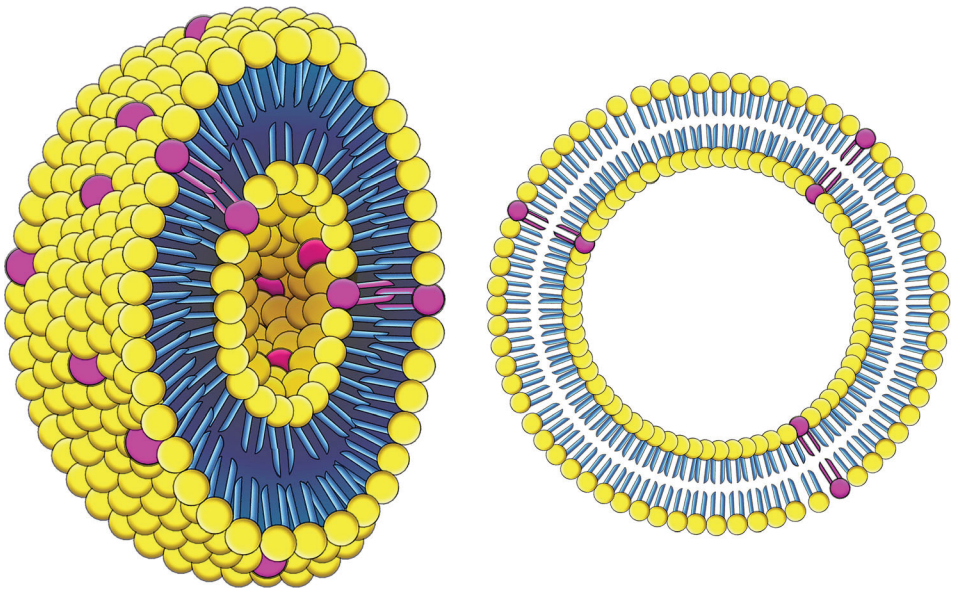

Fig. 4 Liposomal amphotericin B (L-AMB). Amphotericin B Phospholipid

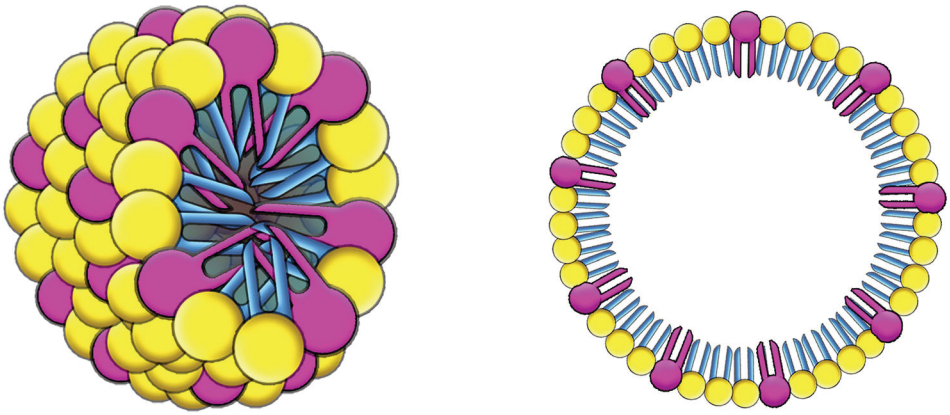

Fig. 5 Amphotericin B deoxycholate (D-AMB). Amphotericin B Phospholipid

PHARMACOKINETICS AND PHARMACODYNAMICS PROPERTIES

The understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of an antimicrobial agent is based on the exposure–response relationship between the drug and the pathogen. Such affinity can be established by integrating PK and PD parameters, such as both maximum concentration (C_{max}) and the area under the curve (AUC), and the minimum inhibitory concentration (MIC), respectively. As a result, optimal drug regimens are achieved, and toxicity and resistance development are minimized [114, 115].

To determine the PK/PD index of an antifungal, in vitro and in vivo studies are performed. In vitro susceptibility tests are needed to determine MIC in reproducible conditions and PK studies to estimate population

parameters (clearance and volume of distribution). At the end, there is a dose–response experiment to relate exposure to the antifungal effect using the drug fractionation [116]. For AMB, it is known that the PK/PD indices were previously determined and their results confirmed by clinical studies which show that optimizing the dose to reach the PD targets leads to greater clinical efficacy [117].

Among lipid formulations, the clinical correlation of potential differences in PD has been difficult to establish because of limitations in determining MIC and differences in models of PK/PD indexes [116]. But, the study by Hong et al. [118], which included nine children diagnosed with fungal infection and treated with L-AMB, found that while C_{max}/MIC = 40 ± 13 produced a partial response, the complete response would need values of 67.9 ± 17 (p = 0.021). Considering the study by Andes et al. that reported D-AMB as five times more potent (C_{max}/MIC = 10), the results with L-AMB could be considered consistent [117].

Anyway, the pharmacokinetics of amphotericin B varies substantially between D-AMB, L-AMB, and ABLC, and its parameters should not be used to predict the behavior of any other AMB formulation [119]. The drug is poorly absorbed by the gastrointestinal tract and must be administered parenterally to treat systemic fungal infections.

As a fungicidal, amphotericin B relies on its concentration to display its antifungal effect. As mentioned before, the ability to reach those concentrations will determine the success of an intervention [120, 121].

According to the current manufacturer of D-AMB, an initial intravenous infusion of 1–-5 mg/day gradually increased by 0.4–0.6 mg/kg/day produces C_{max} ranging from approximately 0.5 to 2 μg/mL, which stabilizes at about 0.5 μg/mL. D-AMB is highly bound to plasma proteins (> 90%) and has an initial half-life of 24 h and an elimination period of 15 days. About two-thirds of plasma concentrations are detected concomitantly in peritoneal, synovial, inflamed pleura, and aqueous fluids and rarely exceed 2.5% in cerebrospinal fluid. Highly resistant fungi may need higher interventions such as 1.5 mg/kg per day, with prolonged infusions over 6 h, compared with 4 h for susceptible species [122–126].

D-AMB concentrations in vitreous humor or normal amniotic fluid are negligible, whereas full details of its tissue distribution are not known. Excretion of the drug is slow though the kidneys, with less than 5% of the dose being eliminated in the active form. The accumulated urine output over a period of 7 days is equivalent to approximately 40% of the amount of drug infused [127].

Balancing the drug's kinetics along with its collateral effects, continuous infusion became one of the main strategies for the treatment of fungal infections with AMB, enhancing tolerability and lowering mortality, whilst reducing infusion-related toxicity [128–130].

LFABs, on the other hand, present a varied pattern in their pharmacokinetics, with primarily data obtained from animal studies. In 1989, Gondal et al. [131] reported peak concentrations five times higher compared to the same dosage of the conventional formulation, after administering 1 mg/kg of L-AMB to mice.

Subsequently, another study also indicated increased L-AMB concentrations in blood, liver, and spleen, while decreased levels were reported in kidneys and lungs [132]. In human beings, results described by Tollemar and Ringdén [133] showed that a dose of 3 mg/kg of the same compound obtained an average C_{max} of 24.3 μg/mL—in accordance with previous studies that reported even greater peaks, varying from 10 to 35 μg/mL [134, 135], but reaching lower concentrations than those produced by other LFABs in liver, spleen, lung, and kidneys—except for the central nervous system [50, 136]. After the administration of 5 mg/kg/day of liposomal amphotericin B, 90 μg/mL peak levels were measured, along with a half-life of 5–10 h [134].

It is presumed that the volume of distribution (V_d) of the liposome is limited by a decreased AMB interaction with membrane proteins and/or cholesterol, thus allowing significantly higher peak concentrations. However, the association of these higher concentrations to an increased antifungal action in vivo is still not determined [137]. Despite these data, the pharmacokinetics of L-AMB remains relatively unclear, but it is a fact

that a liposome composition has a significant impact on the properties of such formulations [138].

The first detailed profile of ABLC's disposition in human beings presented a broad interindividual variability, beyond large tissue distribution and a long-standing half-life time—similar to D-AMB. At standard doses, a C_{max} of 2 μg/mL was registered for the lipid complex [52, 136, 139].

The lipid complex of amphotericin B has a nonlinear dose-dependent kinetics, and, in contrast to the usual pattern, an increased clearance and V_d according to the dosage administered. In multiple schemes, with an interval smaller than $t_{1/2}$, there is little accumulation of the drug in the body [52]. As for tissue levels, different ratios are reported, according to the systems tracked: 0.2× (kidneys and brain), 2× (liver and lungs), and 5× (spleen), when compared to plasma concentrations [136].

Special populations such as pregnant women, elderly, and obese still lack pharmacokinetic studies on their activity [128]. As for neonates, preterm infants, and children, although there is extensive use on these age ranges, pharmacokinetic data and ideal dosage schemes are also scarce and limited, especially for infants under 10 kg [118, 140].

STRUCTURE–ACTIVITY RELATIONSHIP AND DRUG–TARGET INTERACTIONS

As a general rule, the polyenes exert their effect by associating with sterols of the fungal membrane and interrupting their integrity. This association occurs because of the high affinity between the drug and fungal ergosterol, which, after forming pores in its membrane, spills ions out of the cells, resulting in their death. Nevertheless, this affinity is less for human cholesterol, which explains the drug's greater effect on the pathogen than on host cells.

In 1988, Chéron et al. [141] were the pioneers in studying the correlation between AMB derivates and their biological activity. Such compounds represent a unique basis for the study of the antifungal structure–activity relationship and the understanding of its properties [142, 143]. Basically, the four axes that support its structure–activity relationship are (1) the derivation of a hydroxyl group at C-13; (2) the absence of a negative charge in the acid group; (3) the polyene itself; and (4) an ionizable nitrogen [144, 145].

The crucial role of mycosamine and the C-35-OH group in the antifungal activity of AMB has been demonstrated by Gray et al. [146]. They concluded that the antifungal mechanism of action of the drug is through a simple binding to the ergosterol of the fungi cells. However, a study by Tevyashova et al. [147] to evaluate several semi-synthetic derivates of AMB showed that those which contained the C-35-OH group and the mycosamine portion afforded low antifungal activity. This result was attributed to the decisive role of the hydroxyl group, especially its position in the region of C-7 to C-10, in the biological activity of AMB.

As for the hypothesis that the ergosterol binding is fundamental to the antifungal activity, a test performed with a derivate of AMB lacking the mycosamine portion suggested the capacity of the composition to bind to ergosterol, but not to form pores in the membrane. This research concluded that the direct interaction mediated by mycosamine between amphotericin B and ergosterol is necessary to form ion channels and cause the death of fungal cells [148]. Once again, Tevyashova et al. [147] obtained different results, suggesting that the mycosamine group does not play a critical role in the interaction with ergosterol. Therefore, the detailed mechanism of these interactions is not yet clear and needs to be investigated.

In its liposomal formulation, amphotericin B is integrated with the liposome membranes, forming a non-covalent complex between mycosamine (positively charge) and distearoylphosphatidylglycerol (DMPG) (negatively charged), as well as hydrophobic interactions. Liposomes accumulate at the site of infection, adhering to the surface of fungal cells, disintegrating and releasing AMB [149]. The amphotericin B lipid complex, on the other hand, depends on fungal lipases acting on the

formulation to then induce drug release in tissues [150].

MECHANISMS OF ACTION AND IMMUNE RESPONSE

After 60 years of investigation, the mechanisms of antifungal action of are not fully elucidated. However, there are ample consensus and evidence that AMB affects cells in two ways: via ergosterol binding and via oxidative damage.

Ergosterol Binding

Basically, the drug interacts with the lipid bilayer of the membrane through its hydrophobic domains resulting in multimeric pores that increase the permeability of ions (K^+, Ca^{2+}, and Mg^{2+}) and cause intracellular loss and consequent cell death.

The specific mechanisms of pore formation and the AMB membrane entrance remain very unclear. Baginski et al. [30] proposed two hypothetical pathways in which AMB–ergosterol binding can happen. The sequential mechanism assumes that the AMB monomers somehow enter the membrane and form binary complexes with the lipids found there, forming the channels. The one-step mechanism assumes that the AMB supramolecular complexes are first formed on the surface of the membrane and shortly after they enter the membrane, producing a reorganization towards the functional channels. Palacios et al. [151] also later described two different mechanisms for it: the sterol sequestration (membrane destabilization) and the membrane permeabilization (ion depletion).

It is clear that ergosterol is needed in a large number of cellular processes such as endocytosis, vacuole fusion, and stabilization of proteins, and that the formation of pores increases antifungal efficacy; however, it is not essential for the death of fungal cells, since the simple connection and sequestration of ergosterol to AMB is sufficient to damage cells because of the multiple cellular processes in which ergosterol is involved [152, 153]. Other studies corroborate this premise, demonstrating that not only is the formation of pores sufficient to produce cell death but that the chemical modifications in the AMB domains do not affect its antifungal activity [28, 154]. Finally, two studies argue that AMB is able to form channels even in the absence of sterols; however, both agree that the concentration required to form pores in these conditions is much higher than in the presence of sterols [155, 156].

Oxidative Damage

Early studies demonstrated that AMB induces oxidative stress in the cells [157, 158]. More recently, Liu et al. [159] confirmed this through genome-wide expression analysis showing that the drug induces the expression of stress genes. Many other independent studies have been performed but the precise role of AMB's oxidative damage in its antifungal activity remains undetermined [160–165].

Among the possibilities, AMB could act directly as a pro-oxidant and induce the accumulation of reactive oxygen species, which leads to influence of its mitochondrial activity, contributing to the oxidative burst. Consequently, the accumulation of free radicals induces multiple deleterious effects on the essential components of the cell, resulting in cell death [28].

In 1996, Brajtburg and Bolard [166] reported a compilation of revised information about the immunostimulatory properties of AMB. At first the drug induces an immune response predominantly in a proper dose range. The example used came from their study in which AMB increased the immune response in most inbred strains of mice. In addition, its prophylactic use against fungal infections would come from these assumptions, from stimulating the immune system under the appropriate conditions [167]. The article also highlights that although there are experimental studies agreeing with the stimulating effects of AMB on cells of the immune system, the suppression of humoral and cell-mediated immunity, as well as the suppression of macrophage activation, has also been reported.

Thus, the immunomodulatory effect also has been related to the AMB-associated toxicity. Suschek et al. [168] demonstrated that AMB increases the expression of the inducible nitric oxide synthase (iNOS) isoform, producing an increase in nitric oxide (implicated in the processes of vasodilation and protection against pathogens). However, AMB also increases the induction of pro-inflammatory cytokines and it would therefore be related to the drug's toxicity in the host [169].

What is known so far is that the drug interacts with Toll-like receptors (TLR2), inducing the release of pro-inflammatory cytokines including interleukin-6 (IL-6), IL-8, tumor necrosis factor (TNFα), and monocyte chemotactic protein 1 ((MCP-1). On the other hand, its interaction with TLR4 produces the release of IL-10, an anti-inflammatory cytokine [170]. In addition, the binding of AMB to sterols can activate membrane enzymes, such as NADPH oxidase, involved in the oxidative stress pathway, generating the accumulation of free radicals as previously described.

SPECTRUM OF ACTION

Literature about AMB's activity against different fungal specimens is conflicting. Despite being a well-known agent against a number of invasive infections, some clinical practice data support therapeutic failure in species like *Candida albicans* and *Candida parapsilosis* [171–174], previously considered to be fully susceptible [175, 176].

Susceptible

It is common sense that most yeasts and molds are susceptible to amphotericin B. Among the genus *Candida*, the species *Candida tropicalis*, *Candida krusei*, *Candida kefyr*, *Candida famata*, and *Candida guilliermondii* are all considered susceptible [171–174, 176]. In addition, *Cryptococcus neoformans*, *Malassezia* spp., *Saccharomyces cerevisiae, Aspergillus nidulans, Aspergillus niger*, and *Penicillium marneffei* are also designated as responsive [174, 176–179].

Intermediate

Aspergillus terreus, melanized fungi like *Bipolaris* spp., *Exophiala* spp., *Cladophialophora* spp., *Fonsecaea* spp. and *Phialophora* spp. among others, along with some *Paecilomyces* species are reported as intermediate in susceptibility [176–183].

Contradictory

Some inconsistent data is reported on *Scedosporium apiospermum, Aspergillus fumigatus, Aspergillus flavus*, *Trichosporon beigelii*, and *Fusarium* spp. regarding resistance in some isolates and treatment failures [176, 177, 180, 181, 184, 185]. On the other hand, *Candida lusitaniae* has been reported to be resistant; nevertheless, most strains were susceptible in the laboratory [171, 172, 174]. Additionally, difficult culture techniques or poor laboratory data also compromise the susceptibility appraisal, being reported for *Malassezia* spp. and Zygomycetes (*Absidia corymbifera*, *Apophysomyces elegans*, *Cunninghamella bertholletiae*, *Mucor* spp., *Rhizomucor pusillus*, *Rhizopus* spp., *Saksenaea vasiformis*) [180].

Resistant

Previously, *Scedosporium prolificans* and *Sporothrix schenckii* were reported as remarkable resistant species [181, 184, 185]. Nowadays, the most recent guidelines suggests caution with this therapeutic approach, because of other first-line options or limited data. The indication large remains for severe or disseminated disease or when the first-line treatment is unavailable [18, 19]. Among *Candida* species, *Candida auris*, *Candida haemulonii*, and *Candida lusitaniae* are considered resistant [186, 187].

OTHER THERAPEUTIC USES OF AMB

In addition to its antifungal action, evidence also supports the clinical use of amphotericin B in other contexts, as already well established in the treatment of visceral leishmaniasis (L-AMB

formulation), caused by the parasite *Leishmania* ssp. [188]. Its use on cutaneous and mucosal leishmaniasis, on the contrary, is still considered off-label by the US Food and Drug Administration (FDA) [188–191].

Evidence also points to antiprotozoal therapeutic applications with *Trypanosoma cruzi* epimastigotes and many reports with *Naegleria fowleri*, for example. Such reports also show that a mixed therapeutic approach could benefit the patient in both cases [157, 192, 193].

There are also studies that propose AMB as a promising new option as an antiviral agent, as it can affect the structure of cholesterol in viral envelopes and cell membranes, as well as in intracellular organelles. Data from experimental studies on the human immunodeficiency virus (HIV), Japanese encephalitis virus, as well as hepatitis B, herpes simplex, and rubella viruses have been reported [194–197].

MECHANISMS OF RESISTANCE

Fungal resistance mechanisms against AMB are rare, but have been reported, portraying a status where the patient does not respond to a standard therapeutic approach [198]. In 2014 Anderson et al. [199], in order to explain the paucity of clinically relevant microbial resistance against AMB, expanded the classic ion channel model and presented a sterol sponge model, in which AMB exists primarily in the form of an extra-membranous aggregates that physically extracts ergosterol from lipid bilayers. According to those authors, once the molecule may simultaneously perturb all of the cellular processes that depend on membrane ergosterol, a number of mutations would be necessary to provoke a relevant alteration, thus causing resistance [199].

Generally, there are host and microbial factors that interfere directly or indirectly with the immune response against a pathogen that predict the success of an intervention [200]. Important host factors are, for example, the immune status of the patient and presence of indwelling materials and surgical devices—possible vehicles for contaminations and biofilm development that could prevent sufficient concentrations of the drug reaching the infection site [201–203].

As for its mechanism of action, decreases in either the amount of ergosterol in the cell membrane or a change in the target lipid could compromise AMB's performance, as a result of decreasing binding sites [175, 198]. In the same way, any mutations in the ergosterol production pathway could affect the quality of this interaction, resulting in poor kinetics—such as *ERG* genes, required for ergosterol biosynthesis [200].

Candida albicans resistant to amphotericin B and fluconazole, for example, revealed upregulated *ERG5*, *ERG6*, and *ERG25* genes when compared with the wild-type strain. These mutations lead to an accumulation of sterol intermediates and a reduced affinity for AMB [204]. *ERG2* and *ERG3* mutations were also related, carrying a low ergosterol content [205–207]. Promastigotes of *Leishmania donovani* also highlight the importance of sterols, once their absence is related to resistance to amphotericin B [208]. Similar results were obtained from cultures of *C. tropicalis* and *Torulopsis glabrata* of a hematopoietic stem cell transplantation population [209]. *C. parapsilosis, C. lusitaniae, T. beigelii, Malassezia furfur, S. apiospermum*, *S. prolificans, Fusarium* spp., and some strains of *S. schenckii* also demonstrate primary resistance against amphotericin B as a result of those implications [175].

Oxidation resistance through increased catalase activity and incubation under hypoxia were credited for some *C. albicans, A. terreus*, and protoplasts cells [163, 210–212]. Additionally, biofilm formation was reported with *Candida* spp. [207]. Fatty acid composition was also proposed to explain polyene resistance, suggesting that an increased membrane fluidity could interfere with the interaction with amphotericin B. Nevertheless, no significant differences between mutants and wild types were tracked [213, 214]. Alterations of cell wall constituents such as chitin (*C. albicans, Kluyveromyces* spp., and *Schizosaccharomyces* spp.) and binding factors like glucans (*C. albicans, C. tropicalis, A. flavus*) could also determine resistance because of their preliminary role in polyene kinetics; notwithstanding, these

mechanisms are only partially understood [215–219].

Finally, as ergosterol plays an essential role in the yeast cell cycle, stationary-phase cells were related to increased resistance in the exponential phase, a fact that could be associated with reduced chitin synthase activity in the stationary growth phase [216, 220, 221].

Resistance against amphotericin B during therapy is not common and is attributed to an acquired resistance of the pathogen or co-infection with different species [175]. In particular, patients with severe neutropenia or compromised hematopoietic health are likely to face this impasse [222, 223]. Cases of *C. albicans, Candida rugosa, C. lusitaniae*, and *C. guilliermondii* were reported [224–226].

STABILITY

According to the literature, reports of amphotericin B's instability when submitted to unfavorable conditions such as exposure to heat, light, and low pH are commonly found [227]; it is even among the 110 substances liable to degradation in tropical conditions (50 °C and 100% humidity) listed by the World Health Organization (WHO) [228]. Aqueous solutions of AMB, on the contrary, could be more stable for prolonged periods of air and light exposure, if maintained between pH 4 and 10 [23, 229].

A recent study showed insignificant degradation of AMB in the presence of water [230]; this fact could be related to AMB's low solubility in aqueous and neutral pH vehicles. Exposure of AMB to ± 70 °C for up to 7 days did not provoke thermal degradation. In a photolysis experiment, degradation occurred within 7 min after exposition to light, in agreement with previous studies that assessed AMB's stability in dark environments [231].

Wiest et al. [232] documented the stability of amphotericin B (100 μg/mL) in four different concentrations of dextrose injection (5%, 10%, 15%, and 20%), when stored for up to 24 h at 15–25 °C and protected from light. This study raised an important question regarding the administration of the drug in dextrose solutions, with concentrations greater than 5%, which would minimize nutritional deficits and glucose instability in neonates.

Regarding the LFABs, the liposome stability is guaranteed by their small size and the fact that cholesterol and DMPG exhibit a high transition temperature (55 °C), when the preparation naturally tends to collapse, releasing its content [128, 233]. The lipid complex, with its two phospholipids, distestylylphosphatidylcholine (DMPC) and DMPG, has a transition temperature of 23 °C (below body temperature), which suggests that the preparation may disintegrate before reaching the site of action [233].

BIOEQUIVALANCE OR THERAPEUTIC EQUIVALANCE

Pharmacologically, two preparations are considered equivalent if they present the same qualitative and quantitative composition of active ingredients and the same pharmaceutical form. Two pharmaceutical equivalents are defined as bioequivalent when, after administration of the same dosage, their bioavailability does not differ statistically. Once two equivalent pharmaceutical forms are also bioequivalent, theoretically, they can be considered as therapeutically equivalent [233].

With the advent of lipid formulations and the fact that they are related to reduction of toxicity, it became necessary to control these drugs to guarantee the level of tolerance and effectiveness, since any change in manufacturing may affect drug performance [24]. It is known that the lipid composition, charge, and size of these preparations can vary considerably depending on the manufacturer [137]. For instance, the manufacturer of ABLC informs in the package insert that liposomal encapsulation or incorporation in a lipid complex can substantially affect the functional properties of the drug by differing in the chemical composition and physical form of the lipid component [234], which, therefore, already attests to its non-bioequivalence.

In vitro [235] and in vivo animal studies [236] sought to establish a therapeutic

equivalence of the conventional formulation compared to that associated with liposomes, claiming that both had the same antifungal potency. However, it is still questioned whether such preclinical bioequivalence data can be extrapolated in humans. Heinemann et al. [137] discussed the need to demonstrate that a dosage of D-AMB of 1 mg/kg would in fact equate to the same antifungal activity as a dose of L-AMB of 1 mg/kg.

Recently, a study gathered evidence and confirmed that LFABs are not therapeutically equivalent [233]. L-AMB and ABLC data are exposed in relation to C_{max} and area under the curve (AUC), showing evident differences between them (non-standard confidence interval of 90%), once again opposing the definition of bioequivalence.

Yet, recommendations of scientific associations and guidelines clearly state the differences between LFABs when presenting their evidence grid in the treatment of different fungal infections. The guidelines of the Infectious Diseases Society of America (IDSA) declare that L-AMB and ABLC have the same spectrum of activity as D-AMB; however, they have distinct pharmacological properties and frequencies of adverse events [237].

Finally, Cifani et al. [233] summarized why lipid formulations cannot be considered therapeutically equivalent. First, because the preparations are not bioequivalent. Second, because there are not enough controlled clinical trials that compare the effectiveness of the formulations in question. Last of all, because therapeutic equivalence is not supported by worldwide guidelines and consensus as different recommendations are attributed to lipid formulations of amphotericin B in their recommendations.

ASPECTS RELEVANT TO CLINICAL PRACTICE

In the daily routine, AMB is an important resource in severe fungal infections, available as a useful agent against virulent infections such as *A. flavus* and *Scedosporium* spp., often related to refractoriness [238].

Data suggests different applications for the different formulations of AMB, including primary and secondary prophylaxis and in refractory disease, when aspergillosis is suspected or confirmed. As a primary prophylaxis, data supports the use of AMB in hematological malignancies (acute myeloid leukemia with prolonged neutropenia [239–244], acute lymphoblastic leukemia [245], allogeneic hematopoietic stem cell transplantation, HSCT [240]), as a result of a high-risk neutropenic status; invasive infections of the central nervous system [63, 64, 76, 243], pulmonary and extrapulmonary disease [63].

As a secondary prophylaxis, patients with previous invasive infections and undergoing allogeneic HSCT or entering a risk period with non-resectable foci of *Aspergillus* disease benefit from L-AMB [246, 247]. Whereas patients with refractory hematological disease had an improved survival rate with L-AMB 3–5 mg/kg [58, 248, 249] and ABLC 5 mg/kg [238, 249–251].

Amphotericin B toxicity is the barrier that prevents its proper prescription, which can result in the spread of infections and therapy failure [136]. In addition, acute infusion-related reactions often imply the interruption of a complete course of the medication. In this sense, LFABs have brought a significant advance in the treatment of invasive fungal infections, allowing prolonged and higher dosage use when compared to D-AMB. Such formulations have often been used interchangeably, although constant vigilance is necessary given the possibility of significant differences in their effectiveness. One question that remains concerns access to such formulations, since the high cost significantly limits their use in developing countries.

COMBINATION ANTIFUNGAL THERAPY

The application of combined antifungal therapy (CAF) is widely accepted to maximize the antifungal effect through the synergistic effect by attacking the same or different targets in fungal cells [252]. As advantages, in addition to the

Table 2 Evidence-based use of combined antifungal therapy for some fungal diseases

Fungal disease	CAF	Recommendation	References
Invasive aspergillosis	AMB + echinocandin	Patients with hematological malignancies and an elevated galactomannan level Salvage therapy in high-risk patients	[237, 255, 256]
Candidiasis	AMB + flucytosine AMB + fluconazole	Native valve endocarditis; candida CNS infection; azole-resistant *Candida glabrata*, ascending pyelonephritis and fluconazole-resistant candida endophthalmitis	[51, 257]
Cryptococcosis	AMB + flucytosine AMB + fluconazole	CNS cryptococcal infections, especially in HIV-infected patients; transplantation	[258–260]
Mucormycosis	AMB + echinocandin AMB + azoles	Refractory disease	[16]

AMB amphotericin B, *CNS* central nervous system

synergistic effect, the amplitude in the spectrum of action, less risk of toxicity owing to the reduction of the combined doses, and less probability of resistance or tolerance (even without evidence to support this statement) can be mentioned. As disadvantages, antagonistic adverse reactions should be considered, in addition to the higher costs and the possibility of systemic toxicity due to the accumulation of more than one antifungal in the body [253, 254].

Drug interactions (whether synergistic or antagonistic) depend on the type of preparations used in a CAF, on the genus and species of fungi, and, of course, on the timing of drug administration and their doses [252]. Table 2 summarizes the available data on the use of amphotericin B in combination therapy, currently recommended in clinical practice.

FUTURE PERSPECTIVES

Despite the broad spectrum of fungicidal activity, limitations such as parenteral administration, reactions related to infusion, acute and chronic toxicity, and also the dosage limits end up harming the potential clinical use of AMB. Although LFABs exhibit a more favorable tolerability and toxicity profile, they are not free of side effects.

The development of non-invasive formulations of AMB is very challenging because of its low aqueous solubility in physiological pH, permeability through membranes, and tendency to self-aggregate, in addition to its low stability at high temperatures and acid pH [261].

Progress in the development of a new formulation of AMB has been described in the literature, with emphasis on encochleated amphotericin B (Coch-AmB). It is a new formulation composed of phospholipid bilayers precipitated with bivalent cations in a multilayer structure, wrapped in a spiral without internal watery space. Such a structure protects the molecule inside, which makes it more stable and allows its oral administration. The drug is released after the interaction of this new system with the target cells, which open in the presence of low concentrations of intracellular calcium [262].

This new possibility would bring numerous advantages to clinical practice including the avoidance of unnecessary patient hospitalization, expansion of antifungal therapy to developing countries where access to hospitals is

Table 3 Current clinical trials with new approaches to amphotericin B

CTID	Title	Phase	Situation	Last update	Outcome measures	Source
jRCTs041200022	Preoperative eradication of *Candida* colonization using amphotericin B for surgical site infections after high-level HBP surgeries: a phase III randomized parallel-group trial	–	Recruiting	Jun/2020	1. Comparisons of surgical site infections incidence between *Candida* eradication group and non-eradication group - None was reported	http://www.rctportal.niph.go.jp
NCT02273661	Evaluation of a therapeutic strategy including nebulized liposomal amphotericin B (Ambisome®) in maintenance treatment of allergic bronchopulmonary aspergillosis (cystic fibrosis excluded)	II	Completed	Jun/2020	1. Occurrence of first severe clinical exacerbation within 24 months following the attack treatment defined by the onset or worsening of dyspnea aggravating the baseline condition that justified (1) increased inhalation treatments, (2) and/or initiation of systemic corticosteroid treatment (3) and/or hospitalization (4) persisting for more than 7 days – None was reported	http://www.clinicaltrials.gov
NCT03399955	Short course regimens for treatment of PKDL (Sudan)	II	Recruiting	Jan/2020	1. Definitive cure and incidence of treatment-emergent adverse events – None was reported	http://www.clinicaltrials.gov
NCT04031833	Encochleated oral amphotericin for cryptococcal meningitis trial (EnACT)	I/II	Recruiting	Nov/2019	1. Highest dose tolerated without inducing vomiting and evidence of fungicidal activity – None was reported	http://www.clinicaltrials.gov

Table 3 continued

CTID	Title	Phase	Situation	Last update	Outcome measures	Source
NCT04140461	AMB dose for cryptococcal meningitis	III	Not yet recruiting	Oct/2019	1. Number of subjects died at week 48 2. 2-week negative culture and disability – None was reported	http://www.clinicaltrials.gov
NCT02629419	CAMB/MAT2203 in patients with mucocutaneous candidiasis	II	Active, not recruiting	Oct/2019	1. Symptoms of mucocutaneous candidiasis 2. Area under the plasma concentration versus time curve (AUC) 3. Drug concentrations in plasma, urine, and saliva 4. Adverse events, changes in laboratory parameters 5. Other outcomes: long-term adverse events, changes in laboratory parameters 6. Long-term symptoms of mucocutaneous candidiasis – None was reported	http://www.clinicaltrials.gov

Table 3 continued

CTID	Title	Phase	Situation	Last update	Outcome measures	Source
NCT02283905	Amphotericin B and voriconazole for pulmonary blastomycosis	IV	Recruiting	Sep/2019	1. The concentration–time profile of antifungals during treatment relative to the level of susceptibility of the infecting organism 2. Clinical recovery—as assessed by time to defervescence; and white blood cell (WBC) count resolution 3. Clinical recovery—time to discontinuation of mechanical ventilation 4. Clinical recovery—time to respiratory dysfunction resolution – None was reported	http://www.clinicaltrials.gov
NCT04018417	Evaluation of amphotericin B in Optisol-GS for prevention of post-keratoplasty fungal infections	II/III	Withdrawn	Jul/2019	1. Endothelial cell density 2. Incidence of post-keratoplasty fungal keratitis – None was reported	http://www.clinicaltrials.gov

AMB amphotericin Bl, *CTID* clinical trial identification, *HBP* hepato-biliary-pancreatic, *PKDL* post-kala-azar dermal leishmaniasis, *CAMB/MAT2203* encochleated amphotericin B, *HIV* human immunodeficiency virus

difficult, prophylactic use of AMB, lack of side effects related to the infusion, and accessibility to treatment. Finally, with the slower release of the active ingredient, higher concentrations could be achieved in several organs. Table 3 displays the list of the clinical trials from the last 2 years that seek to improve the use of amphotericin B in different situations.

CONCLUSIONS

In the 60 years since it was first marketed, amphotericin B remains the gold standard for the treatment of invasive fungal infections while its lipid formulations have been developed to improve tolerability with a similar spectrum of activity and a more favorable safety profile. However, they have considerably different pharmacological characteristics. Both

ABLC and L-AMB have a distinguished pharmacokinetic profile that determines their efficacy and toxicity. On the other hand, the amphotericin B lipid complex, with a larger particle size, is characterized by a rapid decline in the concentration of AMB after intravenous administration, followed by an extended elimination half-life which contrasts with the higher C_{max} values and AUC, lower volume of distribution, and shorter elimination half-life of the liposomal version.

Even though some experimental tests have been published, guidelines for better bioequivalence studies are lacking since it is essential to characterize both the stability and the pharmacokinetic profile of LFABs and thus ensure that not only patients benefit from these formulations but that professionals are safe to use them.

The development and registration of new formulations that bring improvements in pharmacological and biopharmaceutical characteristics represent expensive and time-consuming tasks but are essential to reduce toxicity and improve drug tolerability. Promising clinical trials stimulate new possibilities for amphotericin B. The goal will be achieved when AMB can be widely distribute at a lower cost and in a non-parenteral version, resulting in numerous benefits for end users.

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3 RESULTADOS

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Sumário

ARTIGO 2

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ORIGINAL RESEARCH ARTICLE

Amphotericin B in Pediatrics: Analysis by Age Stratification Suggests a Greater Chance of Adverse Events from 13 Months of Age Onwards

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Abstract

Background and Objective Amphotericin B deoxycholate (AMB-D) remains an antifungal agent with great therapeutic value in pediatric patients. The currrent consensus is that its use in neonates is safer than in older children. However, childhood presents different periods of development that deserve to be evaluated more precisely. Our goal was to assess the usage profile of AMB-D in stratified pediatric age groups, adapted according to the National Institute of Child Health and Human Development classification.

Methods This retrospective cross-sectional observational study was conducted at a Brazilian tertiary children's hospital between January 2014 and December 2019. Data of patients who received at least two doses of intravenous AMB-D while hospitalized were extracted from electronic health files. Information on patient demographics, underlying diseases and comorbidities, laboratory examinations, fungal infection diagnosis, and AMB-D use were gathered following specific criteria. Nonparametric tests were applied, such as the chi-square test to compare proportions and Fisher's exact test to assess the association between categorical variables or contingency tables.

Results One hundred and twenty-seven (127) medical records were stratified as preterm neonatal (birth <37 weeks postmenstrual age), term neonatal (birth–27 days), infants (28 days–12 months), toddlers (13 months–2 years), early childhood (3–5 years), middle childhood (6–11 years), and early adolescence (12–18 years). The criteria for the indication of AMB-D followed empirical use as the main indication ($n = 74$; 58.26%), proven and probable fungal infection ($n = 39$; 30.71%), and medical suspicion ($n = 14$; 11.02%). *Candida* spp. was the main etiologic agent isolated in cultures, with the highest frequency of *C. albicans* ($n = 18$; 40%), followed by *Candida parapsilosis* ($n = 14$; 31.11%), and *Candida tropicalis* ($n = 6$; 13.33%). Very few acute infusion-related adverse effects were observed during the administration of AMB-D in pediatric patients. We found an unfavorable impact of AMB-D use in patients from 13 months of age onwards suggesting this group as a turning point for a greater chance of adverse events, and not soon after the neonatal period.

Conclusions Clinical or observational studies based on age stratification are essential to accurately elucidate whether potentially toxic drugs can be used safely in the pediatric population. Our search for a turning point was shown to contribute to the accuracy of the study, as it provided data on the impact of D-AMB in specific pediatric age groups.

1 Introduction

After 60 years of use, amphotericin B deoxycholate (AMB-D) remains the treatment of choice for several potentially fatal invasive fungal diseases (IFD), including opportunistic and endemic mycoses, and those affecting the pediatric population [1, 2]. Invasive candidiasis and candidemia remain major causes of morbidity and mortality, notably among immunocompromised and those hospitalized long term [3–7]. Epidemiologically, *Candida* spp. are the most common yeasts and along with other pathogens that cause IFD with potentially high mortality rates and poor response even to new antifungal therapies [7–10].

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Key Points

Most of the original research on amphotericin B deoxycholate in pediatrics goes back decades with some limitations in the number of patients.

To the best of our knowledge, this is the first observational study based on an age-stratification strategy and included a significant number of patients, totaling 127.

Until our findings, the discussion of acute side effects related to the infusion and toxicity of amphotericin B deoxycholate was primarily focused on neonates, with an overall worse scenario in older children.

We found an unfavorable impact of the conventional formulation from 13 months of age onwards, suggesting that this age group is a turning point for a greater chance of adverse events.

With this, we encourage other centers to investigate and support this approach in identifying a more accurate age group to better understand where prescribing amphotericin B deoxycholate is safer or less harmful in pediatrics.

Acute infusion-related side effects (IRSE) and toxicity associated with AMB-D have been widely reported, including renal, hepatic, and hematologic disorders [11, 12]. Nephrotoxic effects are mediated by changes in membrane permeability and vasoconstriction. Infusion-related side effects are believed to be triggered by the release of inflammatory cytokines by mononuclear phagocytic cells. The intensity appears to be related to the availability of the antifungal agent to react with the target cells, regardless of the extent of exposure [13, 14].

Despite their significantly higher costs, lipid-based formulations have been developed to reduce toxicity and used in clinical practice with relatively similar efficacy [15]. Nevertheless, because of undesirable adverse events (AEs) and the availability of new drugs, there is a consensus that AMB-D should be avoided in pediatric patients. However, previous data demonstrated that AMB-D AEs are less prominent in neonates than in older children and adults. Hence, AMB-D remains as the first-line antifungal agent for the youngest population [2, 16, 17]. Studies have indicated that this tolerability is due to the pharmacokinetics of the drug, including higher active clearance rates and a lower volume of distribution, resulting in lower plasma concentrations. However, other studies argue that AEs are directly proportional to the patient's age and AMB-D dosage when compared with other formulations [18–25].

In pharmacovigilance, drug safety has been relatively less explored in children than in adults. However, there is still a lack of data to support the suggested impact of pharmacokinetics on differences in the toxicity of AMB formulations [17]. The available studies are mostly single-center studies with a limited number of patients and focus mainly on neonates [19, 26–29]. Additionally, it is necessary to consider that childhood presents different periods of development that need to be evaluated more precisely. None of the previous publications evaluated the effects of AMB in a robust group of non-neonate patients, nor did they compare the results between different pediatric age groups. Therefore, gaps remain on the safety of drug administration in non-neonate patients.

We characterized and compared the occurrence of AMB-D AEs in different pediatric age ranges to provide more sustainable evidence on this topic and support doctors' decision making. In addition, we assessed the usage profile as well as the impact of AMB-D in stratified age groups, adapted according to the National Institute of Child Health and Human Development classification [30]: preterm neonatal (birth < 37 weeks of postmenstrual age), term neonatal (birth–27 days), infants (28 days–12 months), toddlers (13 months–2 years), early childhood (3–5 years), middle childhood (6–11 years), and early adolescence (12–18 years).

Furthermore, we strived to find a "watershed," a period of age in childhood that could indicate a turning point where the benefit of using AMB-D outweighs the risk. Consequently, lipid-based formulations could be directed for particular ages to reduce toxicity.

2 Material and Methods

2.1 Study Design

We conducted a retrospective cross-sectional observational study between January 2014 and December 2019 involving the medical records of patients who received at least two doses of intravenous AMB-D while hospitalized at a Brazilian tertiary public-private children's hospital. The institution has approximately 400 beds and offers more than 30 services in different specialties, including transplants. This study was approved by the research ethics committee of the hospital, waiving the requirement for informed consent.

We reviewed patients' medical records from registration to discharge or death during their hospitalization for AMB therapy. Data were extracted from electronic health files and collected using REDCap electronic data capture tools hosted at our institution [31, 32]. Information on patient demographics, underlying diseases and comorbidities, laboratory examinations, fungal infection diagnosis, and AMB-D use were gathered following specific criteria.

Proven and probable IFD were classified according to the European Organization for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group consensus group, based on microbiology, imaging, and clinical findings [33, 34]. Additional data were considered in the open field when any information reported by the physician about the patient's daily evolution was relevant.

The present children's hospital was accredited in 2019 at the maximum level (III) by the National Accreditation Organization [35, 36]. Consequently, different methods are used for drug pharmacovigilance, including spontaneous reporting and monitoring prescription events. The spontaneous reporting of AEs plays an important role in drug surveillance for the pediatric population, as a caregiver (usually a parent) monitors all steps at the bedside, from identification to possible reactions that may occur during or after drug administration. In addition, the nursing professional responsible for the infusion of AMB-D remains attentive to acute events and is aware of the potential toxicity of the drug. Any signs or symptoms that may be related to the administration of the antifungal agent should be recorded, in addition to informing the attending physician. Thus, to be true to the identification of AEs and aware of the limitations of the study's retrospective nature, medical records were carefully consulted so as not to omit information mainly on neonatal patients. Acute IRSE occur most frequently with initial doses during administration; thus, nursing records were also checked to avoid missing any notes.

In addition to infusion, renal, hepatic, and other organ functions require monitoring. Each laboratory parameter was analyzed separately for each stratified age group, as the study center had specific reference values for neonates and distinct pediatric age groups. In short, we identified laborarory parameters that were adequate and inadequate immediately before and after AMB-D exposure. Kidney function during AMB-D exposure was evaluated using serum urea, creatinine, and potassium profiles. Similar analyses were performed to identify hepatic and hematologic toxicity using alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, bilirubin, hemoglobin, neutrophils, and platelets as markers.

Amphotericin B dosages at the present study site are recommended on an "mg kg^{-1}" basis. The AMB-D regimen can range from 0.5 to 1.5 mg kg^{-1}/daily for neonates and pediatric individuals. The AMB-D infusion duration may be reduced to a minimum of 2 hours if the 4- to 6-h infusion is well tolerated.

2.2 Statistical Analyses

Data were analyzed using R version 4.1.0, IBM SPSS Statistics for Windows version 25.0, and MedCalc version 20.027 [37–39]. Some values were expressed as the median and range for a continuous variable and as an absolute frequency and percentage of the group from which they were derived. A nonparametric chi-square test was applied to compare proportions and a Fisher's exact test to assess the association between categorical variables or contingency tables (i.e., groups of newborns and non-neonates, occurrence of AEs). We generated descriptive charts using Microsoft Excel® [40] for some significant (considering 5% significance) relevant results.

We also analyzed laboratory parameters to identify whether the drug had a direct impact from the time it was administered. The chi-square test was used to evaluate the toxicity of AMB-D on target organ functions. The measure was the relationship between the number of patients who presented normal values of a given exam adjusted to the reference values of each age group and the total number of patients who underwent the exam in the following period: baseline (the day before the first AMB-D dose), day (D) 3, D7, and D14 of AMB-D therapy, and end of treatment (last day of AMB-D use). The results represent the percentage of adequation for each parameter. Therefore, it was possible to minimize the bias of patients who already had any compromised function before receiving AMB-D.

In some cases, owing to the small sample size of a specific stratified age group, *p*-values were provided for descriptive purposes only. In other cases, for better statistical equality and credibility, we re-divided patients into two groups: neonates and non-neonates. The purpose was to understand if there was any divergence between the groups. Finally, we presented the 95% confidence intervals for *p*-values, and differences in proportions in the tables and graphs, to explain the observed values.

3 Results

3.1 General Data

This study included children aged ≤ 18 years who underwent AMB-D therapy. Initially, 206 medical records were identified. Fifteen records were excluded because of a single exposure to the drug, seven for previous exposure, three for duplicate data, and one for the lack of essential data. Another 53 patients were excluded because they were receiving AMB lipid-based formulation therapy. Patients who started treatment with AMB-D but switched to another AMB formulation after a few days upon medical request were considered, as the first exposure to AMB-D was the most important for the study. In total, 127 medical records were included in the study. Data were stratified by age group to present a more homogenous comparison of variables (Table 1).

The main age group receiving AMB-D therapy was preterm neonates, or birth at < 37 weeks' postmenstrual age, with variation between 24 and 37 weeks of gestational age, corresponding to 35.43% of the total. Eleven were classified as very low birth weight (< 1.5 kg) [1.06–1.36] and ten as extremely low birth weight (< 1.0 kg) [0.620–0.980]. In neonates, the main underlying disease was gastrointestinal disorder (52.8%). Older children present with a frequency of more than 50% for a variety of other conditions, such as cardiological, genetic, ophthalmological, and neurological diseases. Approximately 89% of all patients received AMB-D in the intensive care unit. No significant difference between the sexes was found despite female individuals representing 53.5% of the population treated with AMB-D.

3.2 Invasive Fungal Infection and AMB-D Treatment

Of the 127 medical records analyzed, 35.43% had proven fungal infection, with a survival rate of 66.66%, and no evidence of residual disease after the end of therapy, except for those who had their treatment suspended because of a medical decision to change antifungal therapy ($n = 4$; 3.15%). The median length of hospital stay, daily dosage, and other information are shown in Table 1. The pediatric patients received a maximum AMB-D dosage of 1.5 mg/kg/day. A gradual increase or decrease in dosing for posology adaptation was observed in 67 records (52.7%). The actual number of days of AMB-D use (excluding possible breaks and occasional suspensions with returns during treatment) and its cumulative dose ranged from 3 to 42 days and from 3.30 to 890.50 mg, respectively. When testing the correlation between groups of proven and non-proven fungal infections, we found that in the preterm neonatal age group, it was possible to associate the length of hospital stay (181 days vs 97 days; $p = 0.024$) with the death rate (46% vs 22%; $p = 0.017$).

Considering the criteria for AMB indication, empirical use was the most common ($n = 74$; 58.26%), followed by proven and probable [31, 32] ($n = 39$; 30.71%), and medical suspicion ($n = 14$; 11.02%). Doctors reported the most common diagnoses of proven disease as "sepsis" with 18 cases, "candidemia" with ten cases, and "urinary tract infection" with nine cases (Table 2). *Candida* spp. was the main etiologic agent isolated in cultures, with the highest frequency of *C. albicans* ($n = 18$; 40%), followed by *C. parapsilosis* ($n = 14$; 31.11%), and *C. tropicalis* ($n = 6$; 13.33%). Fungal specimens were isolated from normally sterile sites such as peripheral blood ($n = 32$; 71%), catheter tip ($n = 12$; 26.6%), and central venous catheter ($n = 5$; 11%). Fifteen patients (33.3%) had positive urine culture results. Of the 46 patients with proven IFD, 15 lost their lives. Finally, the 127 patients received antifungal therapy with at least two doses of AMB-D alone (94; 74.01%), or in combination with an azole (24; 18.90%), or an echinocandin (9; 7.09%).

3.3 Searching for a "Watershed" for Greater Occurrence of AEs

Acute IRSEs during AMB-D administration were observed mainly in older children, totaling four occurrences (3.1%). Fever, itching or rash, trembling or chills, and nausea or vomiting were cited. Fifty percent of all patients received prophylactic premedication, including antipyretics, antihistamines, and corticosteroids, to prevent the onset of acute IRSE. The age-stratified Chart 1A shows the respective occurrences of acute IRSE, setting a turning point from toddlers (aged 13 months–2 years). Neonates (preterm and term) and infants (with zero occurrences) were pooled to compare with older children, showing significant associations between the two. Laboratory parameters of toxicity were individually classified as adequate or inadequate according to the age reference value. After a general comparison, another turning point was traced in the toddlers, suggesting a greater chance of target-organ toxicity from this age group forward (Chart 1B).

In our study, toxicity was assessed using the proportion of adequation of urea, creatinine, potassium, and other laboratory parameters. For nephrotoxicity, the urea proportion of adequation for neonates at baseline was 59%, meaning that less than 60% of patients were within normal levels (according to reference values) before receiving AMB-D. The proportion followed D3 (54%), D7 (65%), and D14 (48%) until the end of treatment (52%), with no significant variation during therapy length. However, the same parameter for older children revealed another pattern after AMB-D use, starting with 73.5% of adequation at baseline, followed by a sequence of significant decreases of adequation at D3 (53%), D7 (52%), D14 (31%), and end of treatment (46%) [$p = 0.0055$] (Table 3).

There was no considerable variation in creatinine levels, although a small percentage of patients (12, 9.4%) showed signs of acute kidney injury or developed oliguria/edema. Six belonged to the neonate group: 4/45 (8.9%) preterm neonates and 2/27 (7.4%) term neonates. The other six represented older children: 5/25 (20%) in infants and 1/7 (14.3%) in the early childhood group. For creatinine proportion of adequation, no significant differences were found between the neonates and non-neonates (Table 3). Serum potassium levels showed no significant changes in the neonate group during treatment, apart from an expressive decrease of up to 27% at the end of treatment for older children ($p = 0.0072$). Only a third or less of the laboratory results for the liver function, such as alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, and bilirubin, were available (not shown). Hematological parameters, such

Table 1 Demographic data and clinical characteristics of pediatric patients receiving D-AMB therapy from 2014 to 2019 at a Brazilian tertiary public-private children's hospital divided by age stratification

Variables	Age groups[a] Total *n* = 127; 100%					
	Neonates		Older children			
	Preterm neonatal < 37 wk PMA *n* = 45; 35.4%	Term neonatal Birth–27 d *n* = 27; 21.2%	Infants 28 d–12 mo *n* = 25; 19.7%	Toddler 13 mo–2 y *n* = 9; 7.1%	Early childhood 3 y–5 y *n* = 7; 5.5%	Middle childhood 6 y–11 y *n* = 8; 6.3%	Early adolescence 12 y–18 y *n* = 6; 4.7%
Sex, F/M	28 F 17M	10 F 17 M	15 F 10 M	4 F 5 M	5 F 2 M	3 F 5 M	3 F 3 M
Weight, median (kg) [range]	1.6 [0.6–6]	3.1 [2–7.8]	3.5 [1.2–13]	12.1 [9.5–16]	21 [12–38]	24 [18–74.8]	39 [28–56]
Underlying diseases, *n* (%)							
Diabetes mellitus	–	–	–	–	–	–	–
Hypertension	–	–	2 (8)	–	–	–	1 (17)
Neoplasm/ hematologic disease	–	3 (11)	2 (8)	2 (22)	2 (29)	3 (38)	–
Gastrointestinal disease	29 (64)	9 (33)	11 (44)	1 (11)	1 (14)	–	–
Hepatopathy/ liver disease	1 (2)	2 (7)	–	1 (11)	–	–	1 (17)
Nephropathy/ kidney disease	9 (20)	4 (15)	2 (8)	1 (11)	–	–	1 (17)
Rheumatological disease	–	–	–	2 (22)	–	–	1 (17)
Neurological disease	7 (16)	7 (26)	6 (24)	2 (22)	4 (57)	1 (13)	3 (50)
Immune/autoimmune disease	1 (2)	2 (7)	1 (4)	2 (22)	–	–	–
Solid organ transplant	–	–	–	–	–	1 (13)	1 (17)
Others	11 (24)	15 (56)	16 (64)	5 (56)	2 (29)	3 (38)	2 (33)
HSCT, *n* (%)	–	1 (3.7)	2 (8)	2 (22.2)	–	–	1 (16.6)
Febrile neutropenia, *n* (%)	2 (4.4)	–	2 (8)	1 (11.1)	–	1 (12.5)	–
Fungal disease, *n* (%)							
Possible	32 (71)	12 (44)	15 (60)	5 (56)	2 (29)	4 (50)	6 (100)
Probable	–	1 (4)	–	–	2 (29)	2 (25)	–

Table 1 (continued)

Variables	Age groups[a] Total *n* = 127; 100%						
	Neonates		Older children				
	Preterm neonatal < 37 wk PMA *n* = 45; 35.4%	Term neonatal Birth–27 d *n* = 27; 21.2%	Infants 28 d–12 mo *n* = 25; 19.7%	Toddler 13 mo–2 y *n* = 9; 7.1%	Early childhood 3 y–5 y *n* = 7; 5.5%	Middle childhood 6 y–11 y *n* = 8; 6.3%	Early adolescence 12 y–18 y *n* = 6; 4.7%
Proven	13 (29)	14 (52)	10 (40)	4 (44)	3 (43)	2 (25)	–
LOS median (d) [range]	92 [19–469]	76 [35–429]	95 [13–272]	55 [33–132]	56 [38–153]	76.5 [14–209]	34.5 [10–47]
Deaths, *n* (%)	13 (29)	11 (41)	7 (28)	2 (22)	1 (14)	2 (25)	4 (66)
Department of D-AMB treatment, *n* (%)							
Pediatric ward	–	2 (8.4)	1 (4)	1 (11.1)	2 (28.6)	2 (25)	–
Onco-hemato-logical ward	–	–	–	1 (11.1)	–	3 (37.5)	–
ICU	45 (100)	25 (92.6)	24 (96)	6 (66.6)	5 (71.4)	2 (25)	6 (100)
Other	–	–	–	1 (11.1)	–	1 (12.5)	–
D-AMB dosage median (mg/day) [range]	2 [0.9–6]	3.5 [2.3–7.8]	3.3 [1.2–9]	11.5 [3.3–17]	20.3 [6–38]	18 [15.5–21]	37.5 [15–84]
D-AMB dose accumulated median (mg) [range]	26.4 [3.3–177.8]	40 [6.8–210]	37.6 [10.5–135]	112 [27–247.5]	286.5 [87–420]	304 [162.8–484.5]	259 [100.5–890.5]
D-AMB real number of days use median (days) [range]	12 [3–28]	13 [4–42]	12 [3–29]	11 [3–27]	14.5 [9–21]	16 [7–21]	6.5 [3–13]

d days, *D-AMB* amphotericin B deoxycholate, *F* female, *HSCT* hematopoietic stem cell transplant, *ICU* intensive care unit, *LOS* length of stay, *M* male, *mo* months, *PMA* postmenstrual age, *wk* weeks, *y* years

[a]Adapted from the National Institute of Child Health and Human Development [30]

Table 2 Relation of pediatric patients diagnosticated with proven fungal infections, therapeutical regimens, and outcome

Pediatric age groups[a]		Patient	Medical diagnosis of proven fungal infection[b]	Etiologic agent	Isolated sample[c]	Combined therapy	D-AMB real use (d)	Outcome
Neonates	< 37 wk PMA	1	Disseminated candidiasis	*C. glabrata*	Urine; blood		14	Death
		2	Disseminated candidiasis	*C. albicans*	Blood; cath. tip		12	Death
		3	Fungal sepsis	*C. albicans*	Blood; cath. tip	D-AMB + ECN	58	Death
		4	Fungal sepsis	*Candida* spp.	Blood		25	I.H.D
		5	Fungal sepsis	*C. glabrata*	Blood	D-AMB + ECN	24	I.H.D
		6	Candidemia	*C. albicans*	Blood; cath. tip		23	Death
		7	Fungal sepsis	*C. parapsilosis*	Blood		24	I.H.D
		8	Fungal sepsis	*C. albicans*	Blood	D-AMB + Azole	21	I.H.D
		9	Fungal sepsis	*C. albicans*	Urine		3	Death
		10	Fungal sepsis	*C. parapsilosis*	Blood; cath. tip		6	Death
		11	Fungal UTI	*C. parapsilosis*	Urine	D-AMB + ECN	12	I.H.D
		12	Fungal UTI	*Candida spp.*	Urine	D-AMB + Azole	25	I.H.D
		13	Fungal sepsis	*C. parapsilosis*	Blood; c.v.c; cath. tip		20	I.H.D
	Birth–27 d	14	Fungal sepsis	*C. albicans*	Blood		10	Death
		15	Septic shock	*C. albicans*	Blood; dialysis cath.		14	I.H.D
		16	Candidemia	*C. albicans*	Blood; cath. tip		5	Death
		17	Fungal endocarditis	*C. parapsilosis*	Urine; blood		28	I.H.D
		18	Fungal UTI	*C. parapsilosis*	Urine		8	I.H.D
		19	Fungal sepsis	*Trichosporon asahii*	Blood; c.v.c		25	Death
		20	Fungal UTI	*C. albicans*	Urine	D-AMB + Azole	7	I.H.D
		21	Fungal sepsis	*C. parapsilosis*	Blood	D-AMB + Azole	18	I.H.D
		22	Candidemia	*C. albicans*	Urine; blood		4	I.H.D
		23	Fungal UTI	*C. parapsilosis*	Urine		9	Death
		24	Fungal UTI	*C. tropicalis*	Urine		11	Death
		25	Fungal UTI	*C. albicans*	Urine	D-AMB + Azole	6	I.H.D
		26	Fungal sepsis	*C. albicans*	Blood		14	I.H.D
		27	Fungal sepsis	*C. guilliermondii*	Blood		29	I.H.D
Non-neonates	28 d–12 mo	28	Disseminated candidiasis	*C. tropicalis*	Urine; blood		21	I.H.D
		29	Candidemia	*C. parapsilosis*	Urine; blood; cath. tip		25	Death
		30	Resistant candidiasis	*C. albicans*	Cath. tip; blood	D-AMB + ECN	31	I.H.D
		31	Candidemia	*C. parapsilosis*	Blood	D-AMB + Azole	12	I.H.D
		32	Candidemia	*C. parapsilosis*	Blood; c.v.c; cath. tip	D-AMB + Azole	20	I.H.D
		33	Fungal sepsis	*C. albicans*	Blood	D-AMB + ECN	8	I.H.D
		34	Fungal sepsis	*C. tropicalis*	c.v.c; blood; cath. tip	D-AMB + ECN	13	Death
		35	Candidemia	*C. albicans*	Blood; implemented cath.		27	I.H.D

Table 2 (continued)

Pediatric age groups[a]	Patient	Medical diagnosis of proven fungal infection[b]	Etiologic agent	Isolated sample[c]	Combined therapy	D-AMB real use (d)	Outcome
	36	Candidemia	*C. pelliculosa*	Cath. tip; blood		14	I.H.D
	37	Fungal sepsis	*C. albicans*	Blood		20	I.H.D
13 mo–2 y	38	Candidemia	*C. parapsilosis*	Blood		15	I.H.D
	39	Fungal sepsis	*C. parapsilosis*	C.v.c	D-AMB + Azole	14	I.H.D
	40	Fungal UTI	*C. tropicalis*	Urine		3	Death
	41	Fungal UTI	*C. tropicalis*	Urine		6	I.H.D
3 y–5 y	42	Candidemia	*C. albicans*	Biopsies (not discriminated)	D-AMB + Azole	15	I.H.D
	43	Fungal sepsis	*C. parapsilosis*	Blood		14	Death
	44	Disseminated candidiasis	*C. tropicalis*	Blood	D-AMB + Azole	35	I.H.D
6 y–11 y	45	Fungal septic arthritis	*Acremonium* spp.	Synovial liquid	D-AMB + Azole	21	I.H.D
12 y–18 y	-	-	-	-	-	-	-

C. Candida, *cath* catheter, *c.v.c,* central venous catheter, *d* days, *D-AMB* amphotericin B deoxycholate, *ECN* echinocandin, *I.H.D* improved hospital discharge, *mo* months, *PMA* postmenstrual age, *UTI* urinary tract infection, *wk* weeks, *y* years

[a]Adapted from the National Institute of Child Health and Human Development[30]

[b]Medical diagnosis as described in the reviewed medical records

[c]Sequence of positive samples in laboratory tests over time

as hemoglobin and platelets, also showed significant differences between the neonate and non-neonate groups.

Potentially toxic drugs concomitant with AMB-D were also evaluated. The highest frequency was observed with diuretics (65.3%), followed by vancomycin (61.4 %), mostly in newborns, especially in the preterm group (41.9 %), and toddlers (19.3%). Sixty-one patients were given two or more potentially toxic drugs during AMB-D therapy, following the same characteristics as the groups mentioned above. However, no other significant statistical data on toxicity have been established.

4 Discussion

To date, the discussion of acute AEs related to the infusion and toxicity of AMB-D has primarily focused on neonates, with an overall worse scenario in older children. We found an unfavorable impact of the conventional formulation from 13 months of age onwards, suggesting that this age group is a turning point for a greater chance of AEs. To the best of our knowledge, this is the first observational study based on an age-stratification strategy and included a significant number of patients, totaling 127.

Previously published data suggested that differences in AMB-D toxicity in children arise from the amount administered and should not be based on available toxicity data in adults [41]. Indeed, there is still no clear understanding of at what age the benefit of the drug could overcome the risk of its use, or vice versa, or how to identify the age to foresee possible harm caused by the drug in the pediatric population [17]. Age is considered a potential confounder of many associations, as it is often associated with exposure and conditions in different situations. However, it can be controlled through pairing or stratification [42].

It is challenging to compare our proposal with studies that did not follow the same methodology. Yet, many of the studies shared their findings on toxicity in general pediatric patients (Table 4). Significant events related to drug exposure may not be assessed when studies encompass broad age groups, given the variations in a child's developmental physiological and pharmacological stages. A consensus has accepted that among neonates, the drug is not capable of severe target organ toxicity and has fewer AEs than in older children, implying a limit for safe use from the day of birth to approximately 28–30 days of age [33, 41, 44].

In the neonatal population, IFD is often a cause of death, especially in those with very low birth weight who require more invasive support, and multiple and prolonged courses

A)

Age Groups (n)	Occurrence of infusion-related side effects			Turning point	Occurence, by Group		Fisher's exact test
	Yes	No	% (Yes)		Yes	No	
< 37 weeks PMA (45)	0	45	0.0%	Group A (up to 12 months)	0	97	p-value: **0.0027***
birth - 27 days (27)	0	27	0.0%				
28 days - 12 months (25)	0	25	0.0%				
13 months - 2 years (9)	1	8	11.1%	Group B (13 months or more)	4	26	CI 95%, to p-value: [0 ; 0.4395]
3 - 5 years (7)	1	6	14.3%				
6 - 11 years (8)	1	7	12.5%				
12 - 18 years (6)	1	5	16.7%				

B)

Age Groups (n)	Laboratory parameters adequacy			Turning point	Inadequacy, by Group	Chi-squared test
	Inadequate	Adequate	% (Inadequate)		% Inadequacy	
< 37 weeks PMA (409)	160	249	39.1%	Group A (up to 12 months)	37.8%	p-value: **0.0467***
birth - 27 days (251)	93	158	37.1%			
28 days - 12 months (228)	83	145	36.4%			
13 months - 2 years (91)	39	52	42.9%	Group B (13 months or more)	44.3%	Diference: 6.5% CI 95%, to difference: [0.1% ; 13.0%]
3 - 5 years (70)	27	43	38.6%			
6 - 11 years (82)	36	46	43.9%			
12 - 18 years (57)	31	26	54.4%			

Chart 1 Searching for a turning point after amphotericin B deoxycholate exposure, based on age stratification according to the National Institute of Child Health and Human Development [30]. **A** Percentage of occurrence of infusion-related side effects. **B** Comparison of proportion of laboratory parameters from the reference values of each pediatric age group. *Significant results considering 5% significance. *IC 95%* confidence interval, *PMA* postmenstrual age

of antimicrobial agents. In addition, it is associated with significant morbidity, damage to target organs, and compromised neurological development. In this context, AMB-D has been extensively used to treat neonatal IFD. Retrospective studies published after 2001 concluded that AMB-D delivers a survival rate greater than 75%, with a time to eradication between 6 and 10 days of therapy [23]. Unfortunately, there is a lack of data on older children to confirm the effectiveness and tolerability of the drug.

In our study, 60% of all confirmed diagnoses were neonates with *Candida* spp. accounting for 96.3% of the infections. Gastrointestinal diseases represented the main underlying disease, with extended hospital stays, including some reaching many months or even years of permanence. The survival rate after AMB-D treatment was 66.7%. In the preterm neonatal group, we found a correlation in the length of hospital stay between the subgroups of proven or unproven fungal infection and the mortality rate, indicating longer hospital stays and deaths in the group with proven fungal infection when compared with patients without this diagnosis.

Adverse events of AMB-D in neonates are considerably less common than in older children and adults, resulting from the immaturity of their immune system and low cytokine production [29]. Ages following the neonatal period are poorly evaluated, making it difficult to know how safe the use of AMB-D is in older children. Wilson et al. described a high frequency of chills, fever, and nausea in an age range of 1–17 years [29]. Other authors reported similar symptoms without specifying stages of child development [18, 24]. Therefore, it is difficult to predict the stage at which these symptoms become more frequent in children aged 12 months to 17 years.

Recently, an Australian study appeared to be the first to compare two groups of patients based on age adjusted for "90 days or more" and "less than 90 days" of life. It concluded that the use of AMB-D in younger groups did not determine glomerular toxicity, and acute IRSE only occurred in the group aged > 90 days [18]. However, despite the progress, the heterogeneity in dividing pediatrics into two sample groups prevents the study from drawing more specific conclusions about other parties.

Table 3 Percentage of adequation of each laboratory parameter in the assessment of D-AMB toxicity on target-organ functions

Lab tests	Urea			Creatinine			Potassium		
D-AMB therapy follow-up	Neonates	Non-neonates	*p*-Value	Neonates	Non-neonates	*p*-Value	Neonates	Non-neonates	*p*-Value
% Baseline	58.8	73.5	0.102	77.9	89.6	0.102	52.1	63.8	0.211
% D3	53.6	53.2	0.966	81.8	91.3	0.16	43.5	44.7	0.899
% D7	65	52.4	0.204	90.9	86.1	0.477	50	47.1	0.792
% D14	48.5	31.0	0.164	93.5	89.3	0.567	44.1	26.9	0.174
% EOT	52.2	46.0	0.509	80.6	84.1	0.645	46.8	35.6	0.249
p-value	0.4421	**0.0055*(A)**		0.706	0.4363		0.5435	**0.0072*(B)**	
Lab tests	Hemoglobin			Neutrophils			Platelets		
D-AMB therapy follow-up	Neonates	Non-neonates	*p*-Value	Neonates	Non-neonates	*p*-Value	Neonates	Non-neonates	*p*-Value
% Baseline	68.7	56.6	0.199	46	51.2	0.601	32.8	46.9	0.125
% D3	46.7	56	0.334	46.4	50	0.737	25	48.8	**0.013*(D)**
% D7	60.4	47.2	0.222	53.2	44.4	0.469	36	44.1	0.458
% D14	62.5	40.7	0.098	58.6	65	0.655	53.3	40.9	0.427
% EOT	68.4	46.7	**0.028*(C)**	56	54.8	0.916	38.6	51.3	0.22
p-value	0.9715	0.3308		0.2931	0.7612		0.5028	0.6834	

CI confidence interval, *D-AMB* amphotericin B deoxycholate, *EOT* end of treatment, *Lab* laboratory

The proportion comparison test was defined as the relation between the number of patients who were within the normality standards of a given exam adjusted to the reference values of each age group and the total number of patients who had collected the exam in determined period of D-AMB treatment (baseline, day [D] 3, D7, D14, and EOT). The results are shown in a simplified manner for viewing. The comparison of adequation of the neonates and non-neonates' groups are presented with *p*-values horizontally, at each stage of therapy follow-up; and vertically, analyzing each group itself with *p*-values calculated between baseline and the EOT, reflecting the exposure to D-AMB

(A): *p*-value between baseline and EOT. Difference 27.5% and 95% CI 8.2–44.1

(B): *p*-value between baseline and EOT. Difference 28.2% and 95% CI 7.8–45.6

(C): *p*-value between neonates and non-neonates at EOT. Difference 21.7% and 95% CI 2.5–39.0

(D): *p*-value between neonates and non-neonates at D3. Difference 23.8% and 95% CI 5.0–40.9

Based on our experience with age stratification, it was possible to identify groups that developed acute IRSE, identified as toddlers (aged 13 months–2 years), followed by middle childhood aged (6–11 years), early childhood (aged 3–5 years), and early adolescence (aged 12–18 years). Bringing this added information into clinical practice might be relevant and useful, avoiding a gap in detailed information about the stages of children's development. In addition, prescribing prophylactic premedication to 50% of our patients may also be the reason for better control of IRSE.

The most clinically significant and dose-limiting adverse effect that has long been reported in the literature is nephrotoxicity [18–20, 24, 26–29, 45–52]. Previously, it was associated with increased morbidity, mortality, renal replacement therapy, prolonged hospital stay, higher costs, and important long-term adverse effects in children [43, 53]. Over time, changes in AMB-D administration allowed for better tolerability. For example, sodium intake of 4 mEq/kg/day significantly reduced nephrotoxicity [25].

In our study, nephrotoxicity was tracked through creatinine, potassium, and urea levels, as well as diuresis alterations and edema. We adjusted all reference values for each age group to minimize any bias in patients who already had some compromised functions before receiving AMB-D. For statistical purposes, when analyzing a large group of older children, we found a significant adequation decrease in urea levels at the end of treatment. Specifically, they seem to be the most inadequate from early childhood onwards compared with younger children. Potassium levels also showed a significant decrease in the adequation during AMB-D therapy in older children.

Hepatotoxicity was assessed in only one-third of the patients. Less than 50% of the adequation at baseline was observed for the neonate and non-neonate groups, with no relevant variation during treatment. According to Andrew et al., liver toxicity occurred more frequently with the liposomal formulation than with AMB-D (83% vs 56%). Most of the AEs were of low grade; 35/44 (79.5%) patients had grade I or II alterations for any parameter (bilirubin, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transferase) [18].

Blood disorders, including anemia and thrombocytopenia, have also been reported. However, they were most prominent in patients with previous hematological disarray and tended to decline within the days following therapy [20, 24, 45, 48, 50]. We found a significant difference between groups, with older children achieving a worse scenario of adequation for hemoglobin levels and toddlers indicating a more worrisome onset of a negative impact. Platelets also

Table 4 Overview of previous original studies on D-AMB in the pediatric population

Author	Year/country	Title	Method	Total *n*	Age groups (*n* D-AMB)	Survival/death	Adverse event findings
Wilson et al. [29]	1979/USA	Toxicity of amphotericin B in children with cancer	Retrospective transversal	20	1 y–18 y (20)	NA	Azotemia occurred during 23 of 24 treatment courses Frequent IRSE, anemia, hypokalemia, thrombocytopenia, and neutropenia during D-AMB therapy
Baley et al. [26]	1984/USA	Disseminated fungal infections in very low birth weight infants: therapeutic toxicity	Prospective transversal	10	14 d–4 mo (10) ($\bar{x}$ 28 wk Ga)	4/6	Six out of seven drug toxicity-related infants died Interruption of D-AMB therapy, with reinstitution at a lower dose, showed effectiveness in alleviating anuria
Faix et al. [27]	1984/USA	Systemic *Candida* infections in infants in intensive care nurseries: high incidence of central nervous system involvement	Retrospective transversal	27	11 d–3 mo (12)	12/0	Toxicity is common but usually reversible
Turner et al. [28]	1985/USA	Consequences of candidemia for pediatric patients	Retrospective transversal	45	Premature (8) 3 mo–11 y (3)	3/8	No evidence of nephrotoxicity Two patients had hypokalemia during treatment
Starke et al. [24]	1987/USA	Pharmacokinetics of amphotericin B in infants and children	Prospective transversal	10	17 d (1) 1 mo–8 mo (6) 6 y–15 y (3)	7/3	Most surviving patients had a transient rise, early in therapy, in BUN or Cr levels Other readily identifiable causes of pre-renal azotemia were present and contributed for nephrotoxicity
Baley et al. [19]	1990/USA	Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates	Prospective transversal	13	< 36 wk Ga (12) 40 wk Ga (1)	8/5	Serum Cr value rise significantly during therapy and fell significantly at the end of therapy ($p < 0.05$) Hypokalemia was always transient and responded readily to additional potassium chloride
Butler et al. [45]	1990/USA	Amphotericin B as a single agent in the treatment of systemic candidiasis in neonates	Retrospective transversal	38	14 d–4 mo (36) ($\bar{x}$ 29 wk Ga)	30/8	The addition of flucytosine is unnecessary and could contribute to potential toxicity without a clear benefit D-AMB was tolerated among neonates but monitoring renal function is mandatory

Table 4 (continued)

Author	Year/country	Title	Method	Total *n*	Age groups (*n* D-AMB)	Survival/death	Adverse event findings
Glick et al. [47]	1993/USA	Neonatal fungemia and amphotericin	Retrospective transversal	36	30 d–6 mo	30/6	No evidence of toxicity from this drug regimen and no apparent treatment failures No changes in BUN and Cr before or during therapy and in total urinary output
Driessen et al. [54]	1996/South Africa	Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial	Clinical	24	30 d–6 mo (11)	6/5	Fluconazole showed fewer side effects than D-AMB D-AMB developed high levels of direct bilirubin, ALP, and GGT Five in the D-AMB group had severe thrombophlebitis that progressed to skin abscesses as local side effects
Kingo et al. [49]	1997/USA	Lack of evidence of amphotericin B toxicity in very low birth weight infants treated for systemic candidiasis	Retrospective transversal	22	< 36 wk Ga–30 d (18)	14/4	Two patients had hypokalemia and two had alterations on renal function including decreased urine output Hypokalemia was transient and resolved without treatment Two patients with increased BUN before therapy had no evidence of renal toxicity during therapy
Fernandez et al. [46]	2000/USA	*Candida* meningitis in neonates: a 10-year review	Retrospective transversal	23	< 35 wk Ga (23)	17/6	Nephrotoxicity and electrolyte imbalance can be diminished by careful fluid management Increased BUN or Cr levels for whom D-AMB dosing was altered, rapid normalization of renal function was observed
Linder et al. [55]	2003/Israel	Treatment of candidemia in premature infants: comparison of three amphotericin B preparations	Retrospective transversal	56	≤ 33.5 wk Ga 30 d–6 mo (34)	29/5	No signs of nephrotoxicity or hepatotoxicity with any formulation Renal function normalized in 94.2% of the surviving infants given the lipidic formulation
Holler et. al [48]	2004/USA	Effects of fluid and electrolyte management on amphotericin B-induced nephrotoxicity among extremely low birth weight infants	Retrospective transversal	25	< 26 wk Ga 14–18 d (25)	23/2	D-AMB combined with adequate hydration and higher sodium intakes of >4 mEq/kg per day may provide effective protection against nephrotoxicity among extreme low birth weight infants

Table 4 (continued)

Author	Year/country	Title	Method	Total *n*	Age groups (*n* D-AMB)	Survival/death	Adverse event findings
Jeon et al. [50]	2007/South Korea	A comparison of Ambisome® to amphotericin B for treatment of systemic candidiasis in very low birth weight infants	Prospective historical control multi-center	46	≤ 27 wk Ga 30 d–6 mo (20)	15/5	Ambisome® had lower renal and hepatic side effects 55% of the D-AMB group had a 50% increase in serum Cr level against 21% from the Ambisome® group. 100% increase in serum ALT level was 25% and 65% for the Ambisome® and D-AMB groups
Le et al. [51]	2009/USA	Nephrotoxicity associated with amphotericin B deoxycholate in neonates	Retrospective transversal	92	≤ 41 wk Ga 30 d–6 mo (92)	88/4	Nephrotoxicity was mostly mild and resolved by the end D-AMB does not appear to be associated with lasting measurable nephrotoxicity in neonates
Turcu et al. [52]	2009/USA	Influence of sodium intake on amphotericin B-induced nephrotoxicity among extremely premature infants	Retrospective historical control cohort	37	< 30 wk Ga–30 d (37)	34/3	Premature' with high sodium intake (4 mEq/kg/day) had less D-AMB-induced nephrotoxicity than the historical control group No association was found between hydration and D-AMB nephrotoxicity
Benjamin et al. [20]	2018/USA	A phase 3 study of micafungin vs. amphotericin B deoxycholate in Infants with invasive candidiasis	Clinical	30	< 27 wk Ga (2) ≥ 27 wk Ga (8)	9/1	The most common treatment-emergent adverse events were anemia and thrombocytopenia Both agents were safe and well tolerated
Andrew et al. [18]	2018/Australia	Adverse effects of amphotericin B in children; a retrospective comparison of conventional and liposomal formulations	Retrospective transversal	115	< 90 d (9) > 90 d (67)	NA	No IRSE occurred in children aged <90 d Differences in adverse effects is not as marked in children as reported in adults

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *d* days, *D-AMB* amphotericin B deoxycholate, *Ga* gestational age, *GGP* gamma-glutamyl transpeptidase, *IRSE* infusion-related side effects, *mo* months, *n* total number of patients per study, *NA* not available, *n D-AMB* number of patients who received D-AMB per study, $\bar{x}$ mean, *wk* weeks, *y* years

showed a statistically significant difference between the groups at baseline and D3 of AMB-D treatment, although the neonatal preterm was the most affected during treatment.

Diuretics and vancomycin were potentially toxic drugs concomitant with AMB-D, particularly in neonates in the preterm group. However, it was not possible to establish statistically significant data on these associations. All the patients studied by Andrew et al. who reported nephrotoxicity also received one or two concomitant nephrotoxic drugs [18]. However, Baley et al. reported seven cases of acute oliguria in most patients who were not under or previously exposed to other agents, implying that AMB-D alone was responsible for severe renal failure [26]. Studies by Wilson et al., Holler et al., Le et al., and Turcu et al. found no association between renal toxicity and the concomitant use of nephrotoxic drugs (aminoglycosides, gentamicin, tobramycin, vancomycin, indomethacin, and methotrexate) during AMB-D therapy [29, 48, 51, 52].

We achieved our purpose when all parameters were computed together for comparison between the stratified age groups, possibly because they were previously classified individually as adequate and not adequate. A turning point was observed in the 13 months–2 years old group, suggesting a greater chance of target-organ toxicity and acute IRSE occurrence from this age range onwards. We are unaware of any study that has used this methodology to compare observational data.

Limitations of our study include its retrospective design, missing laboratory data, and an unsatisfactory number of patients when stratified by older age. We also tried to minimize the lack of information about AEs, especially in neonates, by checking all records of doctors and nurses during drug prescription/administration; however, we are aware of the possibility of under-reporting and its impact on statistics.

5 Conclusions

Amphotericin B has been widely used to treat IFD. The literature points out that acute IRSE and toxicity in neonates are not as intense and frequent as in older children and adults, allowing the conventional formulation to be considered as first-line therapy for this population. Original research on this topic dates back decades and mainly consists of a single pediatric group or a limited number of patients separating neonates from older children. Our observational study based on age stratification proved essential to accurately elucidate whether potentially toxic drugs could be used safely in the pediatric population. Based on the National Institute of Child Health and Human Development classification, it was possible to find an unfavorable impact of the polyene drug from 13 months of age, suggesting that this range is a turning point for a greater chance of AEs. We encourage other centers to investigate and support this approach in identifying the childhood age that may indicate or better understand when prescribing conventional AMB-D is safer or less harmful in pediatric patients.

Declarations

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Conflict of Interest/Competing Interests FBC, JLB-C, FdAM, APMV, LS, and FdQ-T have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Ethical approval was granted by the Ethics Committee of Hospital Pequeno Príncipe with the waiver of the consent form due to the retrospective nature of the study and the fact that the data collection form is part of the routine of care. Ethical approval number: 3,803,746.

Consent to participate Not applicable.

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Availability of data and materials The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were also performed by all authors. The first draft of the manuscript was written by FBC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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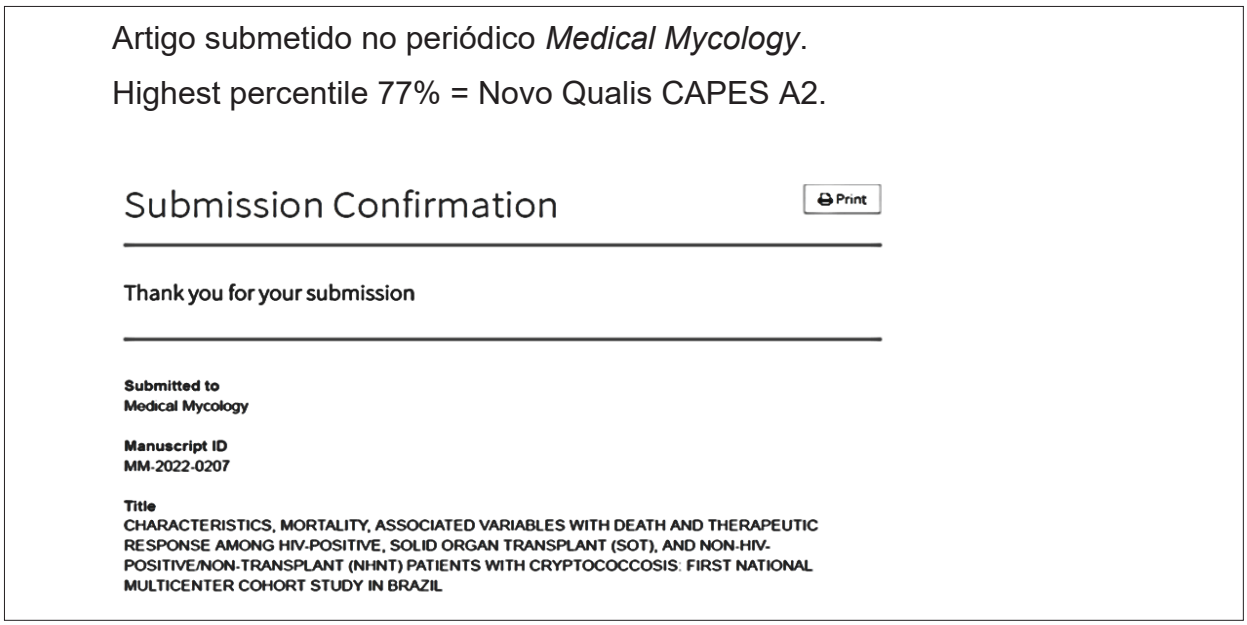

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Sumário

ARTIGO 3

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CHARACTERISTICS, MORTALITY, ASSOCIATED VARIABLES WITH DEATH AND THERAPEUTIC RESPONSE AMONG HIV-POSITIVE, SOLID ORGAN TRANSPLANT (SOT), AND NON-HIV-POSITIVE/NON-TRANSPLANT (NHNT) PATIENTS WITH CRYPTOCOCCOSIS: FIRST NATIONAL MULTICENTER COHORT STUDY IN BRAZIL

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Keyword:	Cryptococcosis, HIV-positive, Solid organ transplant, Non-HIV-positive/non-transplanted, Amphotericin B, Risk factors

Abstract:	Cryptococcosis is traditionally associated with immunocompromised patients but is increasingly being identified in those without the human immunodeficiency virus (HIV) or other immunocompetent individuals. We aim to describe the characteristics, mortality, associated variables with death, and therapeutic response among hospitalized patients with cryptococcosis in Brazil. This is the first multicenter retrospective cohort study conducted in seven public tertiary Brazilian hospitals. Three hundred eighty-four patients were included; the median age was 39, and 283 (73.7%) were men. Hosts were 304 (79.2%) HIV-positive, 16 (4.2%) solid organ transplant (SOT), and 64 (16.7%) non-HIV-positive/non-transplanted (NHNT). Central nervous system (CNS) cryptococcosis had a significantly higher counting level across disease categories, with 313 cases (81.5%). Two hundred and seventy-one (70.6%) patients were discharged home, and 113 (29.4%) died during hospitalization. In-hospital mortality among HIV-positive, SOT, and NHNT was 30.3% (92/304), 12.5% (2/16), and 29.7% (19/64), respectively. Induction therapy with conventional AMB mainly in combination with fluconazole (234; 84.2%) was the most used. Only 80 (22.3%) patients received an AMB lipid formulation: liposomal (n=35) and lipid complex (n=45). Patients with CNS cryptococcosis had lower mortality (83/313, 26.5%) than the other categories (P=0.017). Multivariate analysis showed that age and disseminated cryptococcosis had a higher risk of death [odds ratio (OR), 1.03; 95% Confidence Interval (CI), 1.01 to 1.05; P=0.008 and OR, 1.84; 95% CI, 1.01 to 3.53; P=0.048, respectively]. Understanding the epidemiology of cryptococcosis in our settings will help to recognize the burden and causes of mortality and identify strategies to improve this scenario.

CHARACTERISTICS, MORTALITY, ASSOCIATED VARIABLES WITH DEATH AND THERAPEUTIC RESPONSE AMONG HIV-POSITIVE, SOLID ORGAN TRANSPLANT (SOT), AND NON-HIV-POSITIVE/NON-TRANSPLANT (NHNT) PATIENTS WITH CRYPTOCOCCOSIS: FIRST NATIONAL MULTICENTER COHORT STUDY IN BRAZIL

CRYPTOCOCCOSIS IN IMMUNOCOMPROMISED AND IMMUNOCOMPETENT PATIENTS: DATA FROM A NATIONAL MULTICENTER COHORT STUDY IN BRAZIL

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Abstract

Cryptococcosis is traditionally associated with immunocompromised patients but is increasingly being identified in those without the human immunodeficiency virus (HIV) or other immunocompetent individuals. We aim to describe the characteristics, mortality, associated variables with death and therapeutic response among hospitalized patients with cryptococcosis in Brazil. This is the first multicenter retrospective cohort study conducted in seven public tertiary Brazilian hospitals. Three hundred eighty-four patients were included; the median age was 39 years and 283 (73.7%) were men. Hosts were 304 (79.2%) HIV-positive, 16 (4.2%) solid organ transplant (SOT), and 64 (16.7%) non-HIV-positive/non-transplanted (NHNT). Central nervous system (CNS) cryptococcosis had a significantly higher counting level across disease categories, with 313 cases (81.5%). Two hundred and seventy-one (70.6%) patients were discharged home and 113 (29.4%) died during hospitalization. In-hospital mortality among HIV-positive, SOT, and NHNT was 30.3% (92/304), 12.5% (2/16), and 29.7% (19/64), respectively. Induction therapy with conventional AMB mainly in combination with fluconazole (234; 84.2%) was the most used. Only 80 (22.3%) patients received an AMB lipid formulation: liposomal (n=35) and lipid complex (n=45). Patients with CNS cryptococcosis had lower mortality (83/313, 26.5%) when compared with the other categories (P=0.017). Multivariate analysis showed that age and disseminated cryptococcosis had a higher risk of death [odds ratio (OR), 1.03; 95% Confidence Interval (CI), 1.01 to 1.05; P=0.008 and OR, 1.84; 95% CI, 1.01 to 3.53; P=0.048, respectively]. Understanding the epidemiology of cryptococcosis in our settings will help to recognize the burden and causes of mortality and identify strategies to improve this scenario.

Keywords: Cryptococcosis; HIV-positive; solid organ transplant; non-HIV-positive/non-transplanted; risk factors

Lay summary

In Latin America, the study of cryptococcosis urges it to be increasingly known. This is the first national study in three groups of hospitalized hosts with cryptococcosis in Brazil. Clinical-epidemiological understanding is essential to recognize and improve the current situation in the country.

Introduction

Cryptococcosis is a systemic invasive fungal infection caused by two species complex of the genus *Cryptococcus*, with worldwide distribution and considerable morbidity and mortality. Cryptococcosis especially affects immunocompromised hosts such as human immunodeficiency virus (HIV)-positive and solid organ transplant (SOT) individuals. [1] In addition, cryptococcosis can be identified in a heterogeneous group termed non-HIV-positive/non-transplant recipients (NHNT), characterized by occasional occurrences of this invasive disease in patients with other conditions or diseases or even in immunocompetent hosts. [2]

A recent study estimated that there are globally 152 000 cases of cryptococcal meningitis, resulting in 112 000 cryptococcal-related deaths. [3] It has also been estimated that cryptococcal meningitis is responsible for 19% of acquired immunodeficiency syndrome (AIDS)-related deaths worldwide. The same study also showed that Latin America has the third largest number of cryptococcal meningitis cases, with an estimated 12000 cases in 2020. [3] Brazil and Colombia, followed by

Argentina and Mexico, are the countries with the most cases in Latin America. [4] Regrettably, the burden of cryptococcosis among HIV-uninfected patients is unknown.

HIV-positive individuals have been the most affected by cryptococcosis, particularly in low- and middle-income settings, even in the combined antiretroviral therapy (cART) era. Despite scarce available information, some studies suggest that NHNT individuals recently seemed to outperform HIV-positive patients in some high-income settings, probably due to the increase of immunocompromised populations (i.e. transplant recipients, immunosuppressive therapies) with the highest mortality rates. [5] [6] [7]

The spectrum of hosts with *Cryptococcus* spp. is broad and each group behaves differently according to their immune status, requiring specific interventions and management. In this sense, international guidelines have been making therapeutic recommendations for each group, including the association of antifungal agents to treat cryptococcosis. [2] [8] [9]

Amphotericin B (AMB) remains the main pillar of induction treatment for cryptococcosis, with three formulations available in clinical practice: the conventional deoxycholate amphotericin B (D-AMB) and the lipid formulations as liposomal (L-AMB) and lipid complex (ABLC). The most recent World Health Organization (WHO) guidelines strongly recommend a single high dose of liposomal amphotericin B with 14 days of flucytosine and fluconazole as the preferred induction therapy for managing cryptococcal meningitis. However, in low- and middle-income countries this therapeutical approach is limited mainly because of its high price, lack of registration, and a limited number of quality-assured manufacturers. [9]

The combination of D-AMB with flucytosine is in randomized clinical trials the most fungicidal and effective regimen in HIV-positive individuals with cryptococcal

meningitis compared to D-AMB treatment alone or with high-dose fluconazole. [10] [11] In high-income settings, the combination of L-AMB or ABLC and flucytosine for induction of HIV-positive and SOT individuals with cryptococcal meningitis in a usual scheme of a three-part strategy of induction, consolidation, and maintenance. [2] [12] [13]

However, even though these medications are part of WHO's list of essential drugs, they are not available everywhere, as seen in many African, Asian, and Latin American countries.

Recently, the Brazilian Ministry of Health has provided, through the Unified Health System (SUS), the lipid complex of amphotericin B (ABLC) and/or L-AMB to treat severe cryptococcosis. Nowadays, flucytosine remains not available in Brazil's public sector, but it is expected in late 2022. In this scenario, fluconazole remains the more frequent option for combined antifungal therapy in Brazil. Flucytosine is a key component of antifungal combination therapy, as was demonstrated in a real-world study in our setting. [14]

Despite the high cost, consumption of ABLC has increased in recent years, but evidence of the effectiveness of this specific lipid formulation is limited. [15] [16] [17] [18]

In the present study, we explored the characteristics, mortality, and variables associated with death, in addition to the therapeutic response of different AMB formulations as a single or combined therapy in three groups of hosts diagnosed with cryptococcosis in Brazil.

Methods

Study Design

This is a multicenter retrospective cohort study. [19] The research ethics committee of all centers involved approved the study protocol with a waiver of written informed consent. Data were collected from January 2020 to September 2021.

Data Source

The primary data source was provided by seven Brazilian public or private tertiary hospitals: three are located in the South region, including the coordinating center; two in the Southeast; one in the Central-West, and one in the Northeast region of Brazil (Figure 1). The medical records examined included patients who received free hospital care admitted to one of these centers from January 2014 to December 2019. The coordinating center gathered and managed all data using REDCap electronic data capture tools hosted at Hospital de Clínicas from the Federal University of Paraná State (UFPR). [20][21]

Sample criteria

Medical records of hospitalized patients diagnosed for the first time with any type of cryptococcosis who were treated with any intravenous (IV) formulation of AMB between 2014 and 2019 were included. There was no age, sex, or underlying disease restriction. Patients who were using other antifungals concomitantly were also considered, as well as those who started treatment with an AMB formulation and needed to be changed to another by medical decision.

Possible cases of fungal disease without complete information on the date of diagnosis and/or those who had been exposed to only a single dose of AMB and had already been treated in a previous diagnosis or with recurrence of fungal disease were excluded.

Patients were classified as HIV-positive, solid organ transplant (SOT), and non-HIV-positive/non-transplant recipients (NHNT). Patients were also divided into groups for further analysis: those treated with the D-AMB, L-AMB, and ABLC formulation, as well as any AMB combined with flucytosine or fluconazole.

In the period of this study, the Brazilian Ministry of Health provides only to non-AIDS patients the lipid complex of amphotericin B (ABLC) upon medical proof of fungal disease. The request form is sent along with a copy of the report proving the fungal infection and serology for non-reactive HIV. Patients who, during the treatment period, needed to change an AMB formulation by medical order and had to wait for government approval were considered individually and allocated to the group in which the lipid formulation was used for the longest time. Other cases in which individuals approached half of the treatment with D-AMB and the same amount with some lipid formulation were not considered for statistical analysis.

Disease categories

These include (i) central nervous system (CNS), (ii) pulmonary, and (iii) other extrapulmonary sites. [22] Pulmonary cryptococcosis was defined as patients with a cryptococcal disease involving the lungs with or without another category. CNS cryptococcosis was defined as cryptococcal meningitis with or without another category. Other extrapulmonary sites included those without pulmonary or central nervous system involvement (i.e., skin, disseminated, blood).

The diagnosis of cryptococcosis followed the criteria for proven invasive fungal disease according to Donnelly et al. (2020) and included: 1. Culture, 2. Direct microscopic examination of infected body fluids using Indian ink, 3. Histological examination of tissue samples, and 4. Detection of cryptococcal polysaccharide

antigen in body fluids (CrAg) using latex, enzyme-linked immunoassays, or immunochromatographic tests. Culture on CGB (selective medium L-canavanine glycine bromothymol blue agar) and/or molecular methods were used for the differentiation of *Cryptococcus neoformans* and *Cryptococcus gattii*.

Outcomes

The primary outcome was mortality, defined as the time of the patient's admission to in-hospital death from any cause. Our mortality endpoints during hospital admission were defined as: (1) Short-term (death ≤2 weeks), (2) medium-term (death ≤10 weeks), and long-term (death ≤24 weeks). Secondary outcomes were associated variables with death since hospital admission and discontinuation of AMB-based induction therapy within the first 14 days due to any cause.

Statistical Analysis

Categorical variables were summarized using percentages and analyzed using the chi-squared test. Continuous variables were summarized using medians with dispersion (minimum-maximum) and compared using the ANOVA test or non-parametric Kruskal-Willis test. The promising variables with a plausible biological reason for inclusion in further analysis were verified for normality, using the Shapiro-Wilk & Kolmogorov-Smirnov. Furthermore, for binary variables we set them at 0 or 1 (absent vs present respectively) (Table 1). For the univariate and multivariate analyses of the potential predictors with the outcome - mortality - logistic regression models were adjusted by the variables of interest. The associations between exposure and outcomes were expressed in terms of odds ratio (OR), together with 95% confidence intervals (95% CI). For the analyses of the goodness-of-fit of the model, the C statistic

(area under the receiver operating characteristic curve) and its 95% CI were computed. A 5% level was chosen as a level of significance in all statistical significance tests used. The AIC and McFadden's Pseudo R^2 were calculated to the logistic model. Also, the collinearity statistics were verified to guarantee the tolerance between the variables in the model. All statistical analysis was performed using the software R and JAMOVI. [23]

Results

Of 458 medical records, the final sample consisted of 384 (83.8%) patients first diagnosed with proven cryptococcosis from January 2014 to December 2019. Seventy-four (16.2%) cases were excluded because they had no diagnostic confirmation or incomplete data that did not allow proving the disease. Patients presented a median and [interquartile rate 25th – 75th] age of 39 [31.2 – 48.2] years and 283 (73.7%) of them were men. Most, 304 (79.2%), were individuals HIV-positive, 16 (4.2%) had a history of transplantation, and 64 (16.7%) were NHNT. Main underlying diseases include diabetes mellitus, systemic arterial hypertension, and others, adding up to 22.7% of all comorbidities. The largest number of cases identified occurred in 2018, totaling 79 in the seven centers studied. Differences in the region of study centers were also seen (Table 1).

CNS cryptococcosis had a significantly higher counting level across disease categories, with 313 (81.5%) cases. By further characterizing the groups of patients studied, we found that NHNT (84.4%) was more likely to have CNS cryptococcosis than people HIV-positive (81.9%), even though it was not statistically representative (P=0.0662). On the other side, SOT patients had more pulmonary form infections (31.2%), as compared with HIV+ (3.3%) and NHNT (1.6%). Other extrapulmonary

sites category had HIV-positive and NHNT the same percentage of disease involvement, represented by 14.8% and 14.1% respectively, compared to SOT with 6.2%. Both analyses show significance (P<0.001) (Table 1; Figure 2). *Cryptococcus neoformans* were identified in 215 (56%) cases and *C. gattii* in 17 (4.4%) cases. The remaining 152 (39.6%) cases had no identification at the species level. Two hundred and seventy-one (70.6%) patients left the hospital with a diagnosis of cure or improved discharge and 113 (29.4%) patients died during hospitalization.

Induction therapy in cryptococcosis and amphotericin B formulation trends over time

Because all patients were cryptococcosis first diagnosed, it was possible to follow which initial treatment they were submitted to. Sixty-two patients were using some other antifungal drug in the fourteen days before starting treatment with AMB. Fifty-nine (19.4%) were from the HIV-positive group, one (6.2%) from the SOT, and 7 (11%) from the NHNT. Compared within the AMB therapy groups, the conventional formulation was the most used (278, 77.6%), mainly in combination with fluconazole (234; 84.2%). Lipid formulations together represented 22.3% of AMB prescriptions (Table 2). Sixty-two (17.3%) patients had their prescription changed between formulations, mainly those who started with D-AMB and maintained with some lipid option. The length of AMB therapy in days of use was 20 [14 – 32] days. D-AMB remained as the initial induction therapy for 77.2% of patients over time, despite a trend of increasing use of ABLC in 2018 and a sudden decrease of D-AMB in 2019. In addition, another 13 patients received AMB combined with fluconazole and flucytosine at the same time (not shown).

Ninety-six (26.8%) patients had their treatment suspended/interrupted partially or totally due to renal dysfunction or nephrotoxicity, adverse drug events, death during treatment, or other reasons such as hospital evasion, lack of availability of medication, hospital transfer, and not being informed. Fifty (14%) of them discontinued or had their AMB treatment paused within 14 days of use. Treatment regimens with AMB, considering combined therapy or not, had a mortality rate of 32.4% (90/278) in patients treated with D-AMB, compared to 21.2% (17/80) in both lipid groups (Table 2).

Mortality rates

Overall in-hospital attributable to all-cause mortality was 29.4% (113/384). Thirty-three (8.6%) patients died in the short term (death ≤2 weeks), 98 (25.5%) in the medium term (death ≤10 weeks), and 110 (28.6%) in the long term (death ≤24 weeks). Up to day fourteen had died more NHNT (9.4%) than HIV-positive patients (8.9%). On day seventy of the 304 HIV-positive patients, 81 (26.6%) had died of cryptococcosis, of the 64 NHNT patients 17 (26.6%), and none of the 16 individuals from the SOT group. In long term, the in-patient mortality rate was higher for the HIV-positive (29.6%) than for the NHNT (28.1%) even though the endpoints were not statistically representative (P=0.619) (Table 1).

One of the characteristics of patients who died was age: individuals with a median age of 43 years compared to 38 years with those who were discharged (P<0.002). Another expected data was that more patients died in the Intensive Care Unit than in the infectious disease ward (P<0.001). In addition, patients who were discharged from the hospital had a longer length of treatment than those who died (P<0.001). Other variables comparing both groups are shown in Table 3.

Although most patients belong to the CNS cryptococcosis category (81.5%), they had lower mortality (83/313 or 26.5%) when compared with the other categories [pulmonary 5/16 (31.2%) and other extrapulmonary sites 25/55 (45.4%)] (P=0.017). The therapeutic response could be seen through survival benefits for patients receiving any amphotericin B formulation alone or in combination with fluconazole or flucytosine. However, combination therapy with D-AMB had a higher mortality rate than survival, although there was no statistically significant relationship between them (P=0.537). Also, no significant differences were seen when evaluating the time from admission to an outcome, time from admission to initiation of induction therapy, and time from the end of treatment to outcome between groups (not shown).

Logistic regression model

The multivariate analysis showed that for each additional year of life, individuals had a 3% chance of dying of cryptococcosis (odds ratio, 1.03; 95% CI, 1.01 to 1.05; P=0.008). The analysis also showed a higher risk of death for those who belonged to the 'other extrapulmonary sites' category (odds ratio, 1.84; 95% CI, 1.01 to 3.53; P=0.048). SOT was considering the group with less chance of dying of the fungal disease (odds ratio, 0.18; 95% CI, 0.03 to 0.98; P=0.047). Treatment with any AMB formulation and fluconazole/flucytosine did not impact mortality nor confer a survival advantage in the presented model (Tables 4 and 5).

Discussion

This is the first Brazilian multicenter study of cryptococcosis evaluating several hosts and its main characteristics, mortality, treatment, and variables associated with death. Most patients had HIV infection, CNS involvement was the most common

manifestation of cryptococcosis, most patients received D-AMB-based therapy, and the mortality rate was high. Age and disseminated cryptococcosis were associated variables to death and hosts with SOT were a protector factor of death.

In Latin America, the study of cryptococcosis urges it to be increasingly known, since more than 5,000 individuals are affected with cryptococcal meningitis, and approximately 50% of them eventually died in the region annually. [24] [25]

In the present study, we observed important demographic differences in patients with cryptococcosis among the three groups of hosts. In general, the ages of patients were widely diverse (median 39.2 years; range 3 - 78 years) and men were dominant, especially in the HIV-positive group. HIV-positive patients presented an average of ten years younger than SOT and NHNT patients. Comorbid conditions, such as diabetes mellitus, systemic arterial hypertension, and renal disease were more often identified in the SOT and NHNT groups, probably given their older age. Another characteristic is that SOT recipients were smaller (4.2%) in this study compared to others (10% - 39%). [5] [6] [7] [26]

Some similar studies of cryptococcosis in several hosts have been published. The largest study included 3728 individuals, in a retrospective cohort approach and a multi-center setting. [26] Other studies were carried out in single centers. [5] [6] [7][27] Most of them pooled a sample of 200 - 300 patients, mainly composed of white middle-aged men. [6] [7] [27] Bratton et al. were the only ones that included, most, black men. [5]

Similar to our finding, HIV-positive patients were the most common host in other studies, followed by SOT and NHNT (Table 6). Regarding the clinical presentations, CNS cryptococcosis and disseminated disease were more common in the HIV group, whereas localized pulmonary disease affected mostly NHNT patients. [7]

Most important studies of cryptococcosis in several hosts carried out in the USA reported 90-day mortality rates in HIV-positive patients, SOT individuals, and HNTN, of 14.6-26%, 13.7-24%, and 27-41%, respectively. [6] [7][26] (Table 6). We identified 70-day mortality rates in HIV-positive patients, SOT individuals, and HNTN, of 30.2%, 12.5%, and 29.7%. Thus, the mortality of our HIV-positive patients was higher when compared with the other studies. [6] [7] [26] Mortality of HIV-related cryptococcal meningitis is higher in low- and middle-income countries when compared to high-income countries [28]. This different outcome has several potential explanations, including late testers and late presenters with HIV infection; failures to retain in care of a subset of HIV-positive patients; concomitant anemia, malnutrition, and severe cryptococcal meningitis in vulnerable socio-economical populations; unavailability of point-of-care cryptococcal antigen assays; and restricted access to preferential antifungal therapy, aggressive management of intracranial pressure, and intensive care. [28]

The present study was performed in tertiary centers with a reasonable infrastructure of a middle-income country, but several conditions previously mentioned can be observed.

In this study, performed in six years, the overall in-hospital mortality was 29.4% and SOT individuals present the lower mortality rate (12.5%). Bhatt et al., [29] related in-housel all-cause mortality of 28.1% in a 12-year observational retrospective study performed in Kentucky, USA. Interestingly, in this study, mortality was higher in SOT individuals (5/11, 45.5%) than in HIV-positive patients (6/23, 26.1%) and NHNT groups (21/80, 26.3%), and chronic liver disease was independently associated with mortality.

The annual absolute number of patients receiving conventional or some lipid formulation for initial therapy did not change significantly. This means that D-AMB

remained used as initial induction therapy by nearly 80% of patients over time, despite a trend of increasing use of ABLC in 2018 and a sudden decrease of D-AMB in 2019. Lipid formulations of amphotericin and flucytosine were usually unavailable in Brazil during the period of this study and our results reflected this reality. However, L-AMB and ABLC are being used more frequently in public hospitals in the last few years, and is expected the incorporation of flucytosine in 2022. The results of our multivariate analysis found no association between the therapeutic regimens used for induction and mortality. Probably, the presence of several therapeutic groups with a variable number of patients limited the statistical power of our analysis.

In similar studies to ours, Heavy et al. [7] considered that patients with HIV and SOT tended to receive induction with AMB more than NHNT for disseminated cryptococcal disease. Brizeradine et al. [6] reported that patients with CNS cryptococcosis had no difference in outcomes, but those in the non-CNS group who received fluconazole alone or in combination with D-AMB or an AMB lipid formulation at induction had reduced mortality. Bratton et al. [5] presented their data but did not discuss the associations between medications and mortality. This study points to an increase in the use of L-AMB and to the need for further studies on patient safety when using the conventional formulation.

Randomized controlled trials in HIV-positive patients have shown reduced mortality of cryptococcal meningitis with antifungal combination therapy including flucytosine [10][30] and a better safety profile of L-AMB versus D-AMB [12][31]. There have been no randomized controlled trials of antifungal therapy for cryptococcosis in SOT patients. However, current treatment recommendations are extrapolated from data among HIV-positive patients and observational studies in SOT patients. [32] [12]. Taken together this information, we consider that, if available, lipid amphotericin B plus

flucytosine should be the preferential induction therapy of severe or disseminated cryptococcosis in HIV-positive and SOT patients and probably in HNTN individuals, followed by fluconazole as consolidation therapy. Costs and access to these antifungals are current challenges in Latin America.

In our multivariable analyses, patients with higher age and disseminated disease had a higher risk of death. This result is following other studies. [33] [34] [29] In addition, SOT patients demonstrated decreased odds of mortality compared to HIV-positive and NHNT patients, probably due to the lower frequency of CNS cryptococcosis and higher frequency of localized cryptococcosis in this group of patients. This finding suggests, at least in part, an earlier diagnosis in SOT patients. This is probably because SOT patients are usually under regular outpatient follow-up and in consequence have more timely access to care when compared, for example, to HIV-positive patients who have cryptococcosis in the context of previously undiagnosed advanced HIV disease or previously diagnosed HIV infection but with loss to follow-up and cART discontinuation.

This study has limitations. First, this is a retrospective observational study that comes with intrinsic bias and has inherent limitations in the precision and completeness of the data that may have affected the results. Second, the three study groups were heterogeneous, in particular, SOT had a reduced number of patients which precluded detailed statistical comparisons. Third, antifungal management was non-standard in all centers. However, this study provides valuable information to improve the management of cryptococcosis in a middle-income country in Latin America.

In conclusion, our study shows that HIV infection is the most important condition among patients with cryptococcosis in Brazil, and CNS involvement is the commonest

manifestation in all hosts, mainly HIV-positive and NHNT. The proportion of pulmonary cryptococcosis is relevant in SOT patients. Mortality was high in HIV-positive patients and NHNT hosts. Understanding the epidemiology and characteristic of patients admitted to our hospitals will help to understand the burden and causes of mortality and identify strategies to improve this scenario. Implementation of optimized diagnosis (i.e. lateral flow assay) and treatment (i.e. AMB lipid formulation plus flucytosine) is urgently necessary for Latin America, including Brazil.

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Disclosures of Potential Conflicts of Interest

The authors have no conflicts of interest that are directly related to the content of this article.

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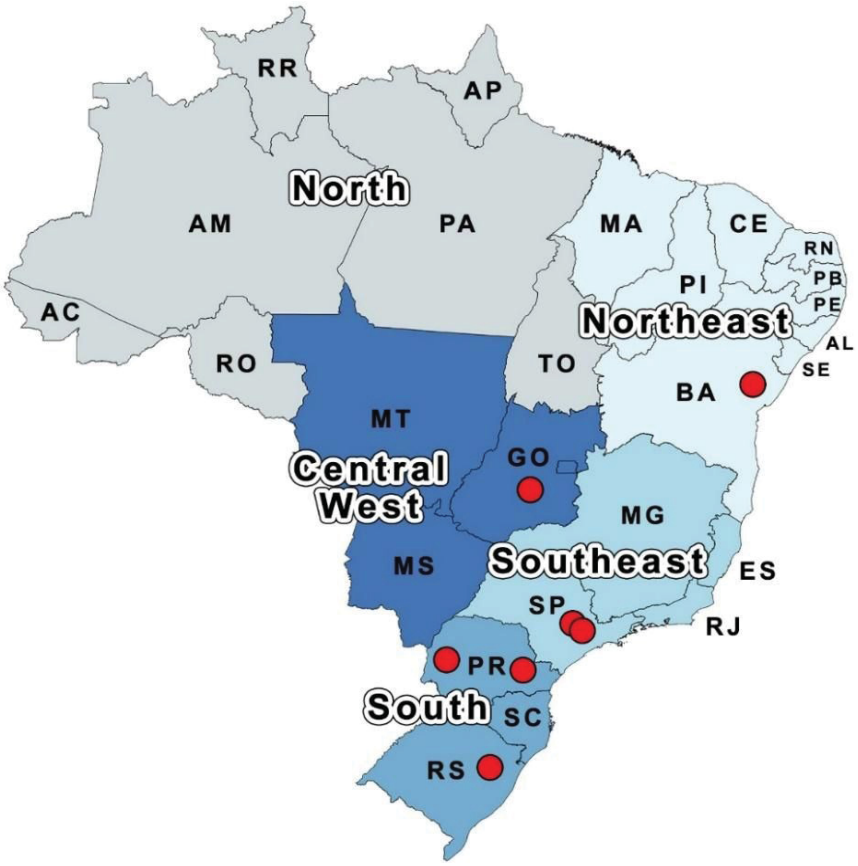

Region	n of centers	n of patients	Classification group (n)
South	3	96	HIV+ (72); SOT (5); NHNT (19)
Southeast	2	90	HIV+ (68); SOT (8); NHNT (14)
Central-West	1	188	HIV+ (162); SOT (0); NHNT (26)
Northeast	1	10	HIV+ (2); SOT (3); NHNT (5)
Total	**7**	**384**	**HIV+ (304); SOT (16); NHNT (64)**

Figure 1. Geographic location of study centers and general data information.

Legend: Each dot represents a public-private tertiary hospital located in four of the five regions of Brazil. There were no study centers located in the North region. HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients; n, number of patients. Created from https://www.mapchart.org.

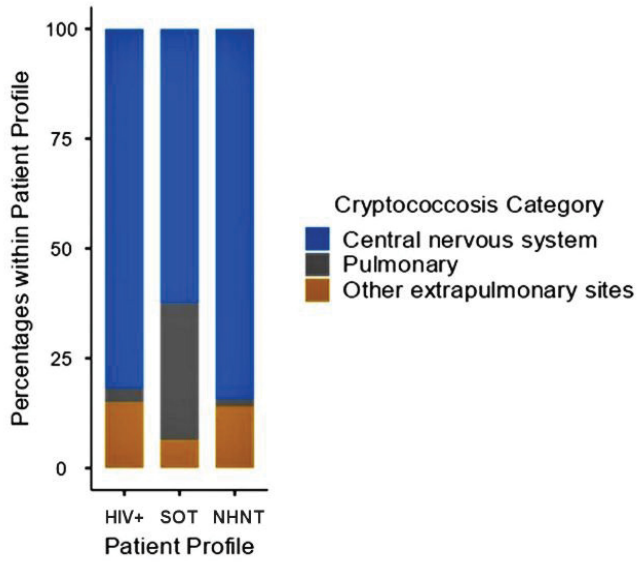

Figure 2. Proportion between hosts and cryptococcal disease.

Legend: HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients.

Table 1. Demographics and other characteristics of 384 patients with cryptococcosis in Brazil.

			Patient Profile						
Variables	**Total (n=384)**	**%**	**HIV+ (n=304)**	**%**	**SOT (n=16)**	**%**	**NHNT (n=64)**	**%**	**P value***
Sex									<.001
Male	283	73.7	237	78.0	7	43.7	39	60.9	
Female	101	26.3	67	22.0	9	56.2	25	39.0	
Age, years									<.001
3 – 17	3	0.8	2	0.6	0	-	1	1.6	
18 – 64	365	95.0	300	98.7	13	81.2	49	76.6	
65 – 78	16	4.2	2	0.6	3	18.7	14	21.9	
Median age [25th – 75th]	39.2 [31.2 – 48.2]		38 [30.8 – 46.2]		48.6 [36.8 – 57.4]		46.7 [34.9 – 61.3]		<.001
Center study region									<.001
Northeast	10	2.6	2	0.6	3	18.7	5	7.8	
Central-West	188	49.0	162	53.3	0	-	26	40.6	
Southeast	90	23.4	68	22.4	8	50.0	14	21.9	
South	96	25.0	72	23.7	5	31.3	19	29.7	
Inpatient and treatment unit									0.204
Infectious disease ward	264	68.8	219	72.0	5	31.3	40	62.5	
ICU	90	23.4	73	24.0	3	18.7	14	21.9	
Others	30	7.8	12	4.0	8	50.0	10	15.6	
Underlying disease									
Diabetes mellitus	20	5.2	7	2.3	6	37.5	7	10.9	<.001
Systemic arterial hypertension	36	9.4	14	4.6	9	56.2	13	20.3	<.001
Hepatic disease	13	3.4	7	2.3	1	6.2	5	31.2	0.053
Renal disease	15	3.9	7	2.3	4	25.0	4	25.0	<.001
Neoplasm / hematological disease	11	2.9	8	2.6	1	6.2	2	3.1	0.057
Neurological disease	19	4.9	11	3.6	1	6.2	7	10.9	0.047
Rheumatological disease	2	0.5	0	-	0	-	2	3.1	0.043
Gastrointestinal tract disease	3	0.8	2	0.6	0	-	1	1.6	0.505

Immunological / autoimmune disease	6	1.6	0	-	1	6.2	5	31.2	<.001
Other	31	8.1	15	4.9	0	-	16	25.0	<.001
Year of first diagnosis									0.160
2014	67	17.4	57	18.7	1	6.2	9	14.1	
2015	66	17.2	55	18.1	2	12.5	9	14.1	
2016	67	17.4	53	17.4	3	18.7	11	17.1	
2017	58	15.1	47	15.5	2	12.5	9	14.1	
2018	80	20.3	61	20.1	2	12.5	17	26.5	
2019	46	12.0	31	10.2	6	37.5	9	14.1	
Cryptococcosis category									<.001
CNS	313	81.5	249	81.9	10	62.5	54	84.4	
Pulmonary	16	4.2	10	3.3	5	31.2	1	1.6	
Other extrapulmonary site	55	14.3	45	14.8	1	6.2	9	14.1	
Skin	2	0.5	2	0.6	0	0.0	0	-	
Disseminated	53	13.8	43	14.1	1	6.2	9	14.1	
Species identification									<.001
Cryptococcus gattii	17	4.4	2	0.6	3	18.7	12	18.7	
C. neoformans	215	56.0	180	59.2	5	31.2	30	46.9	
Not identified	152	39.6	122	40.1	8	50.0	22	34.4	
Outcomes									
Hospital discharge	271	70,6	212	69.7	14	87.5	45	70.3	0.315
Death	113	29.4	92	30.3	2	12.5	19	29.7	0.619
≤ 2 weeks	33	8.6	27	8.9	0	-	6	9.4	
≤ 10 weeks	98	25.5	81	26.6	0	-	17	26.6	
≤ 24 weeks	110	28.6	90	29.6	2	12.5	18	28.1	
≥ 25 weeks	113	29.4	92	30.3	-	-	19	29.7	

Legend: HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients; n, number of patients; ICU, intensive care unit; CNS, central nervous system.

*P value between HIV+, SOT and NHNT: Chi-Square with Fisher correction, ANOVA.

Table 2. General and clinical information according to different amphotericin B therapeutic regimens.

Variables	Total* n= 358 (%)	Treatment groups									P value**
		D-AMB n =24	D-AMB+ FCZ n=234	D-AMB+ 5-FC n=20	L-AMB n =12	L-AMB+ FCZ n=20	L-AMB+ 5-FC n=3	ABLC n =6	ABLC+ FCZ n=28	ABLC+ 5-FC n=11	
Sex											0.006
Male	268 (74.9)	19	179	19	7	14	3	3	18	6	
Female	90 (25.1)	5	55	1	5	6	0	3	10	5	
Age, years											<.001
3 – 17	3 (0.9)	1	2	0	0	0	0	0	1	0	
18 – 64	338 (94.5)	21	227	20	7	20	2	4	27	9	
65 – 78	17 (4.6)	2	5	0	5	0	1	2	0	2	
Median age, [25th – 75th]	39.2 [31.2 – 48.1]	42.4 [30.1 – 60.5]	39.1 [31.9 – 46.9]	32.2 [25.7 – 40.3]	39.2 [33.7 – 47.2]	39.5 [34.9 – 51.2]	43.1 [35.1 – 43.2]	55.3 [30.1 – 72.2]	42.0 [29.6 – 49.2]	35.0 [32.2 – 47.5]	
Center study region											<.001
Northeast]	9 (2.5)	0	0	0	6	1	0	2	0	0	
Central-West	180 (50.3)	18	154	2	0	1	0	0	5	0	
Southeast	78 (21.8)	0	26	18	5	14	3	2	5	5	
South	91 (25.4)	6	54	0	1	4	0	2	18	6	
Patient profile											<.001
HIV+	290 (81.0)	20	214	20	2	10	1	1	18	4	
SOT	15 (4.2)	1	0	0	5	3	1	2	3	0	
NHNT	53 (14.8)	3	20	0	5	7	1	3	7	7	
Cryptococcosis category											0.085
CNS	293 (81.9)	19	202	13	8	16	2	2	25	6	
Pulmonary	13 (3.6)	0	7	0	2	0	0	2	1	1	
OES	52 (14.5)	5	25	7	2	4	1	2	2	4	
Therapy											
AMB trends over time											<.001
2014	64 (17.9)	7	43	1	2	7	0	0	3	1	
2015	65 (18.1)	4	47	3	1	4	0	2	4	0	
2016	58 (16.2)	2	36	12	2	2	1	1	2	0	

2017	53 (14.8)	4	42	3	1	0	0	0	3	0	
2018	74 (20.7)	5	44	1	3	1	0	3	9	8	
2019	44 (12.3)	2	22	0	3	6	2	0	7	2	
Other antifungal usage, 14 days before AMB	62 (17.3)	2	45	1	1	4	0	1	7	1	0.271
Median real days of AMB use, [25th – 75th]	20 [14–32]	17.5 [11.2–25.8]	20.5 [14-32]	22.5 [15.5–31.8]	16 [14-22.3]	16.5 [13.7-22.8]	20 [12-21]	32 [17–34.3]	15.5 [11.5–28.5]	18 [7-42.5]	0.932
Discontinuation or interruption ≤ 14 days by	50 (14.0)	6	27	2	5	2	0	2	3	3	0.056
Renal disfunction or nephrotoxicity	20 (40.0)	1	11	1	3	0	0	1	3	0	0.764
Adverse Drug Event	7 (14.0)	2	2	0	1	1	0	1	0	0	
Death	14 (28.0)	2	10	1	0	0	0	0	0	1	
Other reason	9 (18.0)	1	4	0	1	1	0	0	0	2	
Outcomes											
Hospital discharge	251 (70.1)	11	159	18	10	14	2	5	25	7	0.072
Death	107 (29.9)	13	75	2	2	6	1	1	3	4	0.628
≤ 2 weeks	32 (29.9)	4	24	2	0	0	0	0	1	1	
≤ 10 weeks	93 (86.9)	11	66	0	2	5	1	1	2	3	
≤ 24 weeks	104 (97.2)	13	73	2	2	6	0	1	3	4	
≥ 25 weeks	107 (100%)	-	75	-	-	-	-	-	-	-	

Legend: n, number of patients; D-AMB, deoxycholate amphotericin B; L-AMB, lipossomal; ABLC, amphotericin B in lipid complex; FCZ, fluconazole; 5-FC, flucytosine; HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients; CNS, central nervous system; OES, other extrapulmonary sites; AMB, amphotericin B.

* Discounting 13 patients not allocated to any specific AMB group and another 13 who received AMB combined with fluconazole and flucytosine at the same time.

**P value between D-AMB, L-AMB and ABLC: Chi-Square with Fisher correction, ANOVA.

Table 3. In-hospital mortality of patients with cryptococcosis in Brazil

		Outcomes				
Variables	**Total (n=384)**	**Death (n=113)**	**%**	**Improved hospital discharged (n=271)**	**%**	**P value**
Sex						0.562*
Male	283	81	71.7	202	74.5	
Female sex	101	32	28.3	69	25.5	
Median age, years [25th – 75th]	39.2 [31.2 – 48.2]	43.1 [33.9 – 53.1]		38.0 [30.5 – 47.0]		0.002***
Admission sector						<.001*
Infectious disease ward	264	51	45.1	213	78.6	
Intensive care unit	90	58	58.0	32	11.8	
Underlying disease						
DM	20	7	6.2	13	4.8	0.574*
SAH	36	9	8.0	27	10.0	0.540*
Neurological disease	19	4	3.5	15	5.5	0.411*
Patient profile						
HIV+	304	92	81.4	212	78.2	0.315*
SOT	16	2	1.8	14	5.2	
NHNT	64	19	16.8	45	16.6	
Cryptococcosis category						
CNS	313	83	73.4	230	84.9	0.017*
Pulmonary	16	5	4.4	11	4.1	
OES	55	25	22.1	30	11.1	
Median length of treatment, days [25th – 75th]	20 [14–32]	17 [3 - 66]		26 [3 - 77]		<.001***
Treatment regimen						0.537*
Monotherapy with D-AMB	24	13	12.1	11	4.4	
Monotherapy with any lipid formulation	18	3	2.8	15	6.0	
Combination therapy with D-AMB	254	77	72.0	177	70.5	
Combination therapy with any lipid formulation	62	14	13.1	48	19.1	
Cycle of 14th days of induction therapy completed	272	54	47.8	218	80.4	0.506*

Legend: n, number of patients; DM, *diabetes mellitus*; HAS, systemic arterial hypertension; HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients; CNS, central nervous system; OES, other extrapulmonary sites; D-AMB, deoxycholate amphotericin B.

*Chi-square; **t-test; ***Mann-Whitney

Table 4. Univariable and multivariable logistic regression for the main outcome of mortality.

	Univariable		Multivariable	
Predictor	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (years)	1.03 (1.01 – 1.05)	0.001	1.03 (1.01 – 1.05)	0.008
Sex (Males)	0.86 (0.52 – 1.41)	0.562	0.82 (0.48 – 1.39)	0.467
Patient Profile				
HIV+	1.21 (0.70 – 2.12)	0.401	1.70 (0.89 – 3.27)	0.106
SOT	0.32 (0.07 – 1.47)	0.147	0.18 (0.03 – 0.98)	0.047
NHNT	0.97 (0.53 - 1.75)	0.973	0.72 (0.36 – 1.43)	0.352
Cryptococcosis category				
CNS	1.40 (0.77 – 2.54)	0.263	1.34 (0.70 – 2.57)	0.373
Pulmonary	1.26 (0.42 – 3.73)	0.677	2.02 (0.57 – 7.10)	0.272
OES	2.30 (1.28 – 4.15)	0.005	1.84 (1.01 – 3.53)	0.048
Treatment regimen				
D-AMB + FCZ or 5-FC	0.72 (0.33 – 1.70)	0.422	0.67 (0.26 – 1.69)	0.406
D-AMB	0.69 (0.29 – 1.67)	0.418	0.72 (0.28 – 1.83)	0.501
L-AMB or ABCL	0.33 (0.07 – 1.48)	0.148	0.33 (0.07 – 1.54)	0.160
L-AMB or ABCL + FCZ or 5-FC	0.68 (0.25 – 1.84)	0.449	0.66 (0.23 – 1.90)	0.445
Cycle of 14th days of induction therapy completed				
Yes	ref	-	ref	-
No	1.08 (0.64 – 1.84)	0.752	1.07 (0.60 – 1.92)	0.800

Legend: HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients; CNS, central nervous system; OES, other extrapulmonary sites D-AMB, deoxycholate amphotericin B; L-AMB, lipossomal; ABLC, amphotericin B in lipid complex; FCZ, fluconazole; 5-FC, flucytosine.

Table 5. Comparative effectiveness of therapeutic regimens, as measured by short-term (≤2 weeks mortality), medium-term (≤10 weeks mortality) and long-term (≤24 weeks mortality), related to site of infection among 384 patients with cryptococcosis in Brazil, 2014–2019.

Site of Infection	D-AMB alone, n=24 (%)	D-AMB + FCZ/5-FC, n=254 (%)	L-AMB/ABLC alone, n=18 (%)	L-AMB/ABLC + FCZ/ 5-FC, n=62 (%)
Non-CNS, n=71				
≤2w mortality*, n=13	2 (8.3)	6 (2.4)	1 (5.5)	4 (6.4)
≤10w mortality, n=25	2 (8.3)	15 (5.9)	2 (11.1)	6 (9.7)
≤24w mortality, n=29	3 (12.5)	17 (6.7)	2 (11.1)	7 (11.3)
CNS, n=313				
≤2w mortality, n=34	4 (16.7)	27 (10.6)	0	3 (4.8)
≤10w mortality, n=75	10 (41.7)	55 (21.5)	1 (5.5)	9 (14.5)
≤24w mortality, n=82	10 (41.7)	60 (23.6)	1 (5.5)	11 (17.7)

Legend: *Accumulated mortality. Non-CNS site of infection denotes any site without CNS involvement. CNS site of infection includes patients with CNS only and CNS and non-CNS infection concomitantly. CNS, central nervous system; n, number of patients; D-AMB, deoxycholate amphotericin B; L-AMB, lipossomal; ABLC, amphotericin B in lipid complex; FCZ, fluconazole; 5-FC, flucytosine.

Table 6. Overview of previous original studies on Cryptococcosis based on population groups

Author	Year/ Country	Title	Method/ Setting/ Date	Patient profile (HIV/SOT/NHNT) Total n	Induction therapy with AMB	Mortality rate (n/%) of HIV/SOT/NHNT and time of follow-up			Risk/protective factors (OR 95% CI; P value)
Bratton et al. [5]	2012 USA	Comparison and Temporal Trends of Three Groups with Cryptococcosis: HIV-Infected, Solid Organ Transplant, and HIV-Negative/Non-Transplant	Retrospective Cohort Single-center (1996-2009)	207 (86/42/79)	D-AMB alone D-AMB + 5-FC LFAMB alone LFAMB +5FC Fluconazole Voriconazole None	12 (16) 1y	3 (17) 1y	12 (31) 1y	Severe: hematologic malignancy/ headache, nausea, vomiting, renal insufficiency, liver insufficiency Non-severe: hematologic malignancy/ cough
Brizeradine et al. [6]	2013 USA	Predictors of Mortality and Differences in Clinical Features among Patients with Cryptococcosis According to Immune Status	Retrospective Cohort Single-center (1996-2010)	302 (108/84/110)	D-AMB alone D-AMB + 5-FC LFAMB alone LFAMB +5FC Fluconazole None	20 (19) 90d 28 (26) 1y	14 (17) 90d 20 (24) 1y	29 (27) 90d 38 (35) 1y	Cryptococcemia (5.09, 2.54 – 10.22; 0.001) Baseline CSF opening pressure >25cm in water (2.93, 1.25 – 6.88; 0.013)
George et al. [26]	2017 USA	Comparative Epidemiology and Outcomes of Human Immunodeficiency virus (HIV), Non-HIV Non-transplant, and Solid Organ Transplant Associated Cryptococcosis: A Population-Based Study	Retrospective Cohort Multi-center (2004-2012)	3728 (2091/1470/167)	NA	305 (14.6) 90d 409 (19.6) 1y	201 (13.7) 90d 361 (24.6) 1y	34 20.7 90d 46 (27.8) 1y	Liver disease, congestive heart failure, and lymphoma or leukemia were risk factors for death in both HIV infected and NHNT patients. Liver disease and having received a lung transplant were risk factors for death in the SOT group.
Hevey et al. [7]	2019 USA	Presentation and Mortality of Cryptococcal Infection Varies by Predisposing Illness: A Retrospective Cohort Study	Retrospective Cohort Single-center (2002-2017)	304 (105/41/158)	AMB 5-FC Fluconazole Other azole None	16 (15) 90d	5 (12) 90d	65 (41) 90d	-
Bhatt et al. [27]	2021 USA	Changing demographics and risk factors for cryptococcosis: A 12-year review at a tertiary care centre	Retrospective Cohort Single-center (2005 – 2017)	114 (23/11/80)	4 weeks of IV AMB with or without 5-FC or high dose FCZ ≥ 800mg/day	6 (26) 90d	5 (45) 90d	21 (26) 90d	Age (1.05, 1.01-1.09; 0.013) Chronic liver disease (3.58, 1.32 – 10.15; 0.013)

Legend: HIV+, positive human immunodeficiency virus; SOT, solid organ transplant; NHNT, non-HIV-positive, non-transplant recipients; AMB, amphotericin B; USA, United States of America; D-AMB, deoxycholate amphotericin B; LF AMB, lipid formulation of amphotericin B; FCZ, fluconazole; 5-FC, flucytosine; y, year; d, day; CSF, cerebrospinal fluid.

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Highest percentile 71% = Novo Qualis CAPES A3.

Focus on effectiveness, tolerability, and safety among different amphotericin B formulations in Brazilian patients intended-to-treat invasive fungal infections: a real-life multicenter study

Sumário

ARTIGO 4

CLINICAL THERAPEUTICS

FOCUS ON EFFECTIVENESS, TOLERABILITY, AND SAFETY AMONG DIFFERENT AMPHOTERICIN B FORMULATIONS IN BRAZILIAN PATIENTS INTENDED-TO-TREAT INVASIVE FUNGAL INFECTIONS: A REAL-LIFE MULTICENTER STUDY

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ABSTRACT

(As required by *Clinical Therapeutics*, max 400 words)

Purpose: Data on real-life use of amphotericin B lipid complex (ABLC) formulation compared to others available are limited. The purpose was to evaluate the effectiveness, tolerability, and safety of different amphotericin B (AMB) formulations administered intravenously in the context of hospital practice for the treatment of invasive fungal infections (IFI) and bring a better insight into the role of ABLC.

Methods: This is a multicenter, comparative, retrospective study conducted at ten tertiary Brazilian hospitals. Patients first-exposed to any formulation of AMB intended to treat IFI who had received at least two doses of intravenously administered were eligible. Retrospective data (from January 2014 to December 2019) were extracted from patients' medical files. Clinical parameters were noted pre- and post-treatment to determine effectiveness; Infusion-related reactions and drug interruption to determine tolerability; Adverse events, toxicity, and treatment interruption were stated to analyze safety.

Findings: Overall, 1879 patients who received at least two doses of any formulation of AMB were identified. The median duration of treatment was 14 [7 - 21] days. The overall success rate was 63% (95% CI 60 – 65). ABLC proved to be more effective among the formulations with 53% (95% CI 46.1 – 59.9) within complete response (P=0.039). This was significantly higher in patients who received the drug for a longer duration, ≥4 weeks (88.2% [95% CI 62–98]) compared with <1 week treatment (43.5% [95% CI 31–57]) (P<0.001). Acute infusion-related side effects (IRSE) were observed in 446 patients, with the deoxycholate formulation representing 40%, the lipid complex 29.4% and the L-AMB 12% of them. Six cases (1.3%) of severe IRSE in pediatrics and 10 (2.2%) in adults resulted in treatment discontinuation. Regarding safety, 637 (33.9%) patients presented some alteration in creatinine levels during AMB exposure and 89 (14%), had to interrupt or discontinued the drug within the first 14 days of therapy due to renal dysfunction or nephrotoxicity. Overall mortality reached 34%.

Implications: The lipid complex of amphotericin B is an effective formulation in the treatment of invasive fungal infections as demonstrated, with few adverse events leading to drug discontinuation or any lethal outcome. Furthermore, potential benefits of treating IFIs with a lipid formulation rather

than a conventional one to avoid toxicities became clear. Worse outcomes were observed in patients with short duration of treatment, which implies enforcing a minimum duration of 14 days for the treatment of IFIs in clinical practice.

Keywords: Antifungals; Polyene; Therapeutical response; Toxicity.

INTRODUCTION

Invasive fungal infections (IFIs) are progressively increasing worldwide and have been held accountable for higher morbidity and mortality rates among susceptible patients. [DRGONA 2014, GOW, 2022] At large, the growing number of individuals undergoing immunosuppression therapies, the emergence of antimicrobial resistance, and the toxicity of funded therapeutical agents, especially amphotericin B deoxycholate (D-AMB), highlighted the urgency to establish competitive lines of treatment, able to mitigate and interrupt the natural course of these diseases, without imputing further deterioration of the clinical status of patients. In this sense, lipid-based formulations of amphotericin B (LFABs) emerged as a promising option to be heeded.

Despite the same active ingredient, they differ in pharmacological characteristics such as structure, shape, size, composition, and toxicity - when compared to the conventional formulation. [CAVASSIN, 2021] Liposomal amphotericin B (L-AMB) and the lipid complex of amphotericin B (ABLC) allow the administration of higher doses and vary in efficacy and toxicity depending on the preparation and the species of fungus. The approval of these formulations was based on their comparison with D-AMB mainly in clinical trials. [MEUNIER, 1991], [ORAVCOVÁ, 1995], [SHARKEY, 1996], [ADEDOYIN, 1997], [ELLIS, 1998], [BODHE, 2002]

In pharmacovigilance, drug safety has been relatively less explored in children than in adults. However, there is still a lack of data to support the suggested impact of pharmacokinetics on differences in the toxicity of AMB formulations [PAPPAS, 2016]. In pediatrics, the available studies are mostly single-center studies with a limited number of patients and focus mainly on neonates. [BALEY, 1990][BALEY, 1984][FAIX, 1984][TURNER, 1985][WILSON, 1979] Additionally, it is necessary to consider that childhood presents different periods of development that need to be evaluated more precisely. [CAVASSIN, 2022]

The Brazilian Ministry of Health provides, through the Unified Health System (SUS), the lipid complex formulation to hospitalized patients upon medical proof of fungal disease. Its consumption has increased considerably in recent years, but evidence of the effectiveness of this specific lipid formulation is limited. The most recent guidelines on the management of fungal diseases predict the use of ABLC against yeasts such as *Pseudozyma* spp., *Trichosporon* spp., *Candida* spp., and

filamentous fungi as *Fusarium* spp., black fungi, phaeohyphomycetes, and dematiaceous fungi. Also endemic infections such as coccidioidomycosis, emergomycosis, paracoccidioidomycosis, and invasive fungal infections in patient's refractory or intolerant to conventional therapy (D-AMB) or when L-AMB is not available. [PAPPAS, 2016], [HOENELIG, 2018], [CORNELY, 2019] [CHEN, 2020], [THOMPSON, 2020]

Nevertheless, the limitations of the study designs that attested to its interchangeability and the high cost of its administration have prevented the expansion of its prescription in countries where it is most needed. [BORBA 2018, TONIN 2017] The available protocols and recommendations regarding the treatment of IFIs rely on the conventional formulation and are cautious about the indication of new formulations. [PAPAS, 2016], [HOENELIG, 2018], [CORNELY, 2019] [CHEN, 2020], [THOMPSON, 2020]

In Brazil, there are few studies available regarding ABLC's efficacy. A limited success rate for the treatment of visceral and mucosal leishmaniasis was reported [TUON, 2018], [SANTOS, 2019], while paracoccidioidomycosis [PEÇANHA 2016] and cryptococcal meningitis [TUON 2019] had better results, reaching healing good rates and a better tolerance when compared to D-AMB.

In summary, the drug congregates a broad spectrum and fungicidal activity while promising less toxicity, which made it a reliable option to treat seriously ill patients with invasive infections, who had their treatment interrupted due to adverse events (AEs) or formal contraindications to D-AMB, such as previous renal disease. Despite the clinical advantages of lipid formulations, the optimal choice between them is still not well established. In this sense, the current retrospective study aimed to evaluate the real-life effectiveness, tolerability, and safety among the available AMB formulations to treat IFIs in Brazil.

METHODS

Study Design and Treatment

This multicenter, comparative, retrospective study was conducted in ten tertiary hospitals of four different regions in Brazil: five are located in the South region, including the coordinating center; three in the Southeast; one in the Central-West, and one in the Northeast region of Brazil (Figure 1).

Amphotericin B (AMB) was administered according to clinicians' usual clinical practice, and data on all outcome measures were extracted from patient's medical files and recorded using REDCap electronic data capture tools hosted at Hospital de Clínicas from Federal University of Paraná State (UFPR). [HARRIS, 2009], [HARRIS, 2019]

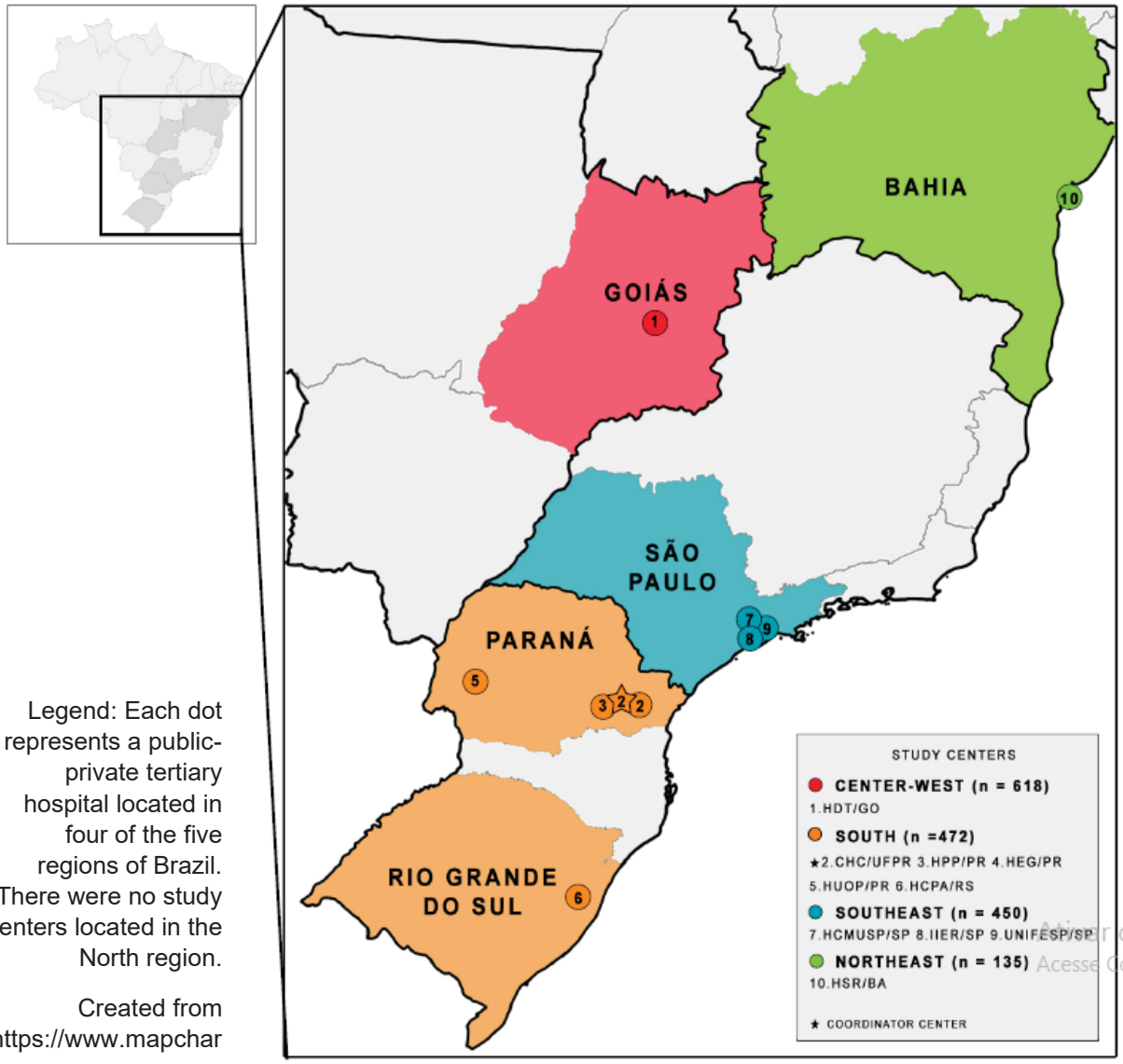
The recommended dose range of AMB is for deoxycholate formulation 0.25 – 1.0 mg/kg/day; for liposomal formulation 3.0 – 5.0 mg/kg/day; and for lipid complex 1.0 – 5.0 mg/kg/day which can be modified or increased up for severe or refractory disease. [DUTCHER, 1959], [ASTELLAS PHARMA, 2022], [TEVA PHARMA, 2020] The recommended duration of treatment also depends on the fungal infection and can vary according to the severity of the disease and the patient's condition. The observational period was the time before the first dose of AMB (identified as baseline) until the end/discontinuation of treatment (last day of AMB administration).

Patients

The study evaluated patients who had received at least two doses of intravenously administered AMB between January 2014 and December 2019 (a full six-year period). Patients (male or female) aged zero (0) years or more who were prescribed any formulation of AMB for possible, probable, or proven invasive fungal infection (according to the Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium [EORTC/MSG] criteria) were considered for participation. [DONNELLY, 2020] There was no age, sex, or underlying disease restriction. However, for the analysis, we stratified age (in years) in groups of pediatric (0 – 17 complete) and adults (18 – 87). Patients using other antifungals concomitantly were also considered, as well as those who started treatment with an AMB formulation and needed

to be changed to another by medical decision. Records that indicated previous use of AMB in a period of six months, use of AMB for the treatment of leishmaniasis, and missing and/or unclear data were excluded.

Figure 1. Geographic location of study centers



Legend: Each dot represents a public-private tertiary hospital located in four of the five regions of Brazil. There were no study centers located in the North region.

Created from https://www.mapchar

Patients were grouped as 1. HIV-positive, 2. Onco-hematologic, 3. Hematopoietic stem cell transplantation (HSCT), 4. Solid organ transplant (SOT) and 5. Immunocompetent, to minimize any bias towards population profile.

The research ethics committee of all centers involved approved the study protocol with a waiver of written informed consent. Data were collected from January 2020 to September 2021.

Disease Characteristics

Assessments performed included the overall diagnoses certainty (i.e., possible, probable, proven), the nature of IFI (i.e., *Fusarium* sp. or any other, if confirmed), any underlying disease, the duration of treatment, laboratory parameters, imaging, and mycological examinations. The improved hospital discharge and cure or mycological evidence of pathogen clearance were subsequently evaluated at the end/discontinuation of treatment and used to inform considerations for the primary endpoint. These criteria were performed according to the judgment of the treating physician.

Outcome Measures

Effectiveness

The primary endpoint was the overall success rate, which was defined as the proportion of patients with complete/partial responses that received the diagnosis of cure or improved hospital discharge after AMB exposure. The proportions of patients who had failed treatment (disease progression or refractoriness) in addition to deaths were also calculated.

Subgroup analyses were conducted to evaluate the effectiveness and impact of ABLC and the other formulations according to the patient profiles (HIV-positive, onco-hematologic, HSCT, SOT, immunocompetent), diagnostic certainty (possible, probable, proven), the main etiologic agent isolated in culture (i.e. *Cryptococcus* spp., *Candida* spp., *Histoplasma* spp.), treatment duration (<1, ≥ 1 to < 2 weeks, ≥ 2 to < 4 weeks, and ≥ 4 weeks) and combined therapy (ABLC alone; plus azole, flucytosine or echinocandin).

Tolerability and Safety

The secondary endpoints included identifying acute infusion-related side effects (IRSE) and their incidences. Open camp with any report by the physician or nurse about IRSE that occurred during or immediately after AMB administration during all treatment periods was included in the analysis. Also, adverse effects (AEs) were defined as events that were, in the opinion of the

investigator, possibly or probably to be related to AMB treatment. Drug interruption was additionally taken into consideration to determine tolerability Measures to evaluate safety included a review of clinical notes, laboratory results, and electrocardiography (ECG) results conducted before (baseline) and during treatment (Day 3, 7, 14, and end of AMB treatment). Any clinically relevant changes in these parameters were recorded for investigation. AEs, dialysis, or any toxicity identified during an AMB course that began before initiation of the drug were attributed to another drug or underlying condition, as appropriate. If occurred after AMB initiation and it was suggestively assigned to the polyene.

Statistical Analyses

For the effectiveness analyses, the primary population was the full analysis set defined as all patients whose records showed that they had received at least two doses of any AMB formulation and had an effectiveness assessment. Complimentary analyses also considered combination antifungal therapy, dosage, and length of treatment of AMB. The tolerability and safety analyses considered all patients who received any formulation of AMB and had no infusion-related reactions, drug interruption, or any toxicity during treatment, and if any, momentary or reversible case.

All data were reported descriptively, using means accompanied by asymptotic 95% confidence intervals (CI) to indicate precision. The effect of treatment duration and dose on the overall treatment success rates was analyzed using a chi-square test or Fisher correction for the cases where a zero was present. For the continuous variables, we applied the ANOVA test to validate the difference between the means in groups of interest; P values less than 0.05 were required for the difference between the two groups to be considered significant. Analyses were performed using R version 4.2.1. [R CORE TEAM, 2019] Bar-plots were constructed with the ggplot2 library for graphical data.

RESULTS

Overall, data from 1952 patients were screened, and 73 were excluded, resulting in 1879 patients who had received at least two doses of intravenously administered amphotericin B between January 2014 and December 2019, with a median [25th – 75th] age of 5 [0.6 – 11.8] years for pediatrics and 41 [31.9 – 52.2] for adults; 1217 (64.7%) of them were men. Most, 759 (40.4%), were HIV-positive patients, 632 (33.6%) were onco-hematologic, 188 (10.0%) had a history of hematopoietic stem cell transplantation, 71 (3.8%) had a history of solid organ transplantation, and 436 (23.2%) did not belong to any of these categories being classified as immunocompetent. The main underlying diseases were *diabetes mellitus*, systemic arterial hypertension, and kidney disease, which accounted for 22.6% of all comorbidities. Other clinical-demographic characteristics are summarized in Table 1.

Around half of the patients had a proven IFI diagnosis (902; 48%), while the remaining cases were possible (685; 36.5%) or probable (292; 15.5%) (Table 1). Of the confirmed cases with positive cultures, 694 (77%) were performed before the decision on the initial therapy for AMB was made. Other diagnostic tests used for IFI investigation included mycological direct examination (422; 22.5%), serological, antigen, or rapid tests (584; 31.1%), and histopathology (297; 15.8%). Nine hundred seventy-two (51.7%) patients undergo imaging examinations (data not shown).

In-hospital mortality reached 34%. Proven cases totaled 298 deaths. The ascending order of IFI in deaths was by *Aspergillus* spp. (63%), *Fusarium* spp. (47.8%), *Candida* spp. (37.8%), *Cryptococcus* spp. (31.5%), *Histoplasma* spp. (27.1%), Others (25.4%) and *Paracoccidioides* spp. (11.5%).

Table 1. Patients Characteristics

	Patient Profile											
Variables	**Total (n= 1879)**	**%**	**HIV+ (n=759)**	**%**	**Onco-Hematologic (n=632)**	**%**	**HSCT (n= 188)**	**%**	**SOT (n=71)**	**%**	**Immunocompetent (n=436)**	**%**
Sex Male	1216	64.7	567	74.7	377	59.7	112	59.6	36	50.7	252	57.8
Pediatrics	323	17.2	6	0.8	205	32.4	47	25.0	8	11.3	103	23.6
Adults	893	47.5	561	73.9	172	27.2	65	34.6	28	39.4	149	34.2
Sex Female	663	35.3	192	25.3	255	40.3	76	40.4	35	49.3	184	42.2
Pediatrics	255	13.6	3	0.4	146	23.1	34	18.1	7	9.9	96	22.0
Adults	408	21.7	189	24.9	109	17.2	42	22.3	28	39.4	88	20.2
Age, years												
0 – 17	578	30.8	9	1.2	351	55.5	81	43.1	15	21.1	199	45.6
Pediatrics median age [25th – 75th]	5 [0.6 – 11.8]		14 [0.9 – 14.7]		8 [3.6 – 13.3]		10 [5.48 – 14]		9 [3.3 – 14.4]		1 [0.08 – 2.1]	
18 – 64	1195	63.6	736	97.0	245	38.8	103	54.8	47	66.2	190	43.6
65 – 87	106	5.6	14	1.8	36	5.7	4	2.1	9	12.7	47	10.8
Adults median age [25th – 75th]	41 [31.9 – 52.2]		39 [31.5 – 46.7]		45 [30.2 – 57.5]		37 [26.8 – 49.8]		50 [36.6 – 59.7]		50 [37.4 – 61.7]	
Pediatrics median weight, Kg [25th – 75th]	17.6 [7 – 37.8]		28.0 [10.1 - 30]		26.5 [13.9 - 43]		32.7 [17.1 – 52.8]		26.4 [16.3 – 44.2]		3.3 [2.02 - 12]	
Adults median weight. Kg [25th – 75th]	61.8 [52.4 - 71]		59.8 [50 – 69.1]		68.7 [58.3- 77.8]		70.0 [57.8 – 78.1]		63.7 [51.8 – 74.3]		64.3 [55 - 74]	
Center study region												
Northeast	135	7.2	12	1.6	75	11.9	26	13.8	17	23.9	37	8.5
Central-West	618	32.9	526	69.3	18	2.8	0	0.0	0	0.0	86	19.7
Southeast	450	23.9	88	11.6	286	45.3	63	33.5	26	36.6	50	11.5
South	676	36.0	133	17.5	253	40.0	99	52.7	28	39.4	263	60.3
Underlying disease												
Diabetes mellitus	106	5.6	17	2.2	33	5.2	9	4.8	21	29.6	37	8.5
Systemic arterial hypertension	212	11.3	40	5.3	64	10.1	20	10.6	35	49.3	76	17.4
Hepatic	65	3.5	18	2.4	8	1.3	3	1.6	16	22.5	26	6.0
Renal	108	5.7	17	2.2	29	4.6	8	4.3	28	39.4	35	8.0
Neurological	85	4.5	12	1.6	9	1.4	2	1.1	2	2.8	62	14.2
Rheumatological	20	1.1	0	0.0	3	0.5	0	0.0	0	0.0	17	3.9
Gastrointestinal tract	96	5.1	5	0.7	6	0.9	2	1.1	2	2.8	83	19.0
Immunological / autoimmune	48	2.6	1	0.1	14	2.2	15	8.0	2	2.8	28	6.4
Other	238	12.7	31	4.1	46	7.3	18	9.6	11	15.5	150	34.4
Median length of stay [25th – 75th]	34 [20 – 55]		27 [17 – 44]		36 [20 – 57]		46 [32 – 71]		47 [28 – 76]		45 [27 – 78]	

Neutropenia												
Febrile	308	16.4	14	1.8	277	43.8	70	37.2	6	8.5	12	2.8
Non-febrile	33	1.8	4	0.5	26	4.1	10	5.3	1	1.4	2	0.5
Non-neutropenic	1538	81.9	741	97.6	329	52.1	108	57.4	64	90.1	422	96.8
Diagnostic certainty												
Possible	685	36.5	185	24.4	320	50.6	92	48.9	20	28.2	163	37.4
Probable	292	15.5	119	15.7	111	17.6	41	21.8	13	18.3	52	11.9
Proven	902	48.0	455	59.9	201	31.8	55	29.3	38	53.5	221	50.7
IFI identification when proven, genera level												
Cryptococcus spp.	336	32.1	268	25.6	11	1.1	1	0.1	12	1.1	53	0.0
Candida spp.	262	25.0	18	1.7	113	10.8	23	2.2	14	1.3	117	11.2
Histoplasma spp.	155	14.8	141	13.5	6	0.6	0	0.0	1	0.1	9	0.9
Aspergillus spp.	35	3.3	8	0.8	18	1.7	12	1.1	3	0.3	8	0.8
Paracoccidioides spp.	26	2.5	7	0.7	2	0.2	0	0.0	4	0.4	14	1.3
Fusarium spp.	22	2.1	1	0.1	18	1.7	8	0.8	0	0.0	3	0.3
Others	59	5.6	5	0.5	36	3.4	14	1.3	4	0.4	17	1.6
Outcomes												
Improved hospital discharge	1234	65.7	488	64.3	415	65.7	96	51.1	50	70.4	288	66.1
Death	639	34.0	266	35.0	217	34.3	92	48.9	21	29.6	147	33.7

Legend: HIV+, HIV-positive; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplant; Kg, kilograms.

The general median duration of amphotericin B treatment was 14 [7 – 21] days and the median daily dose – depending on the formulation – used was 0.9 [0.7 – 1] mg/kg for D-AMB; 3.2 [3 – 4.3] mg/kg for L-AMB and 4.6 [3.8 - 5] mg/kg for ABLC. Seven hundred thirty (38.8%) patients were using some other antifungal drug in the fourteen days before starting treatment with AMB. One hundred ninety-one (25.2%) from the HIV-positive group, 397 (62.8%) from the onco-hematologic, 138 (73.4%) from HSCT, 24 (33.8%) from SOT, and 124 (28.4%) from the immunocompetent group.

Showing a brief comparison among the AMB therapy parties, the conventional formulation was the most used (1042, 55.4%), mainly in combination with an azole (377; 36.2%). Lipid formulations together represented 32% of AMB prescriptions (L-AMB n= 222 and ABLC n= 379). Two hundred thirty-six (12.6%) patients had their prescription changed between formulations, mainly those who started with D-AMB and maintained with some lipid option (Table 2). Of those who had the formulation changed by medical decision, 70 (29.2%) were from the HIV-positive group, 82 (34.7%) from the onco-hematologic, 15 (6.4%) from HSCT, 9 (3.8%) from SOT, and 42 (17.8%) from the immunocompetent group.

Table 2. Amphotericin B regimens of 1879 patients allocated in ten Brazilian tertiary hospitals.

			Treatment Groups								
			D-AMB n= 1042		L-AMB n= 222		ABLC n= 379		Formulation changed		P value
Variables	TOTAL n= 1879	%	Monotherapy n= 626	%	Monotherapy n= 139	%	Monotherapy n= 209	%	n = 236	%	
Sex Male	1216	64.7	402	64.2	69	49.6	132	63.2	144	61.0	0.015*
Sex Female	663	35.3	224	35.8	70	50.4	77	36.8	92	39.0	
Age, years											
0 – 17	578	30.8	267	42.7	29	20.9	68	32.5	84	35.6	<.001*
18 – 64	1195	63.6	342	54.6	89	64.0	117	56.0	135	57.2	
65 – 87	106	5.6	17	2.7	21	15.1	24	11.5	17	7.2	
Center study region											<.001*
Northeast	135	7.2	5	0.8	47	33.8	40	19.1	10	4.2	
Central-West	618	32.9	302	48.2	0	0.0	4	1.9	59	25.0	
Southeast	450	23.9	150	24.0	75	54.0	46	22.0	50	21.2	
South	676	36.0	169	27.0	17	12.2	119	56.9	117	49.6	
Patient profile											
HIV+	759	40.4	288	46.0	9	6.5	12	5.7	70	29.7	<.001*
Onco-Hematologic	632	33.6	166	26.5	73	52.5	128	61.2	82	34.7	<.001*
HSCT	188	10.0	4	0.6	46	33.1	60	28.7	15	6.4	<.001*
SOT	71	3.8	3	0.5	24	17.3	18	8.6	9	3.8	<.001*
Immunocompetent	436	23.2	175	28.0	36	25.9	57	27.3	42	17.8	0.358*
Inpatient AMB treatment unit				0.0							
ICU	703	37.4	265	42.3	62	44.6	90	43.1	82	34.7	0.148*
Infectious disease ward	643	34.2	224	35.8	14	10.1	17	8.1	81	34.3	<.001*
Onco-hematological ward	374	19.9	109	17.4	40	28.8	70	33.5	48	20.3	<.001*
Pediatric ward	33	1.8	17	2.7	2	1.4	4	1.9	3	1.3	0.530*
Other	126	6.7	11	1.8	21	15.1	28	13.4	22	9.3	<.001*
AMB trends over time											<.001*
2014	340	18.1	136	21.7	39	28.1	13	6.2	40	16.9	
2015	288	15.3	91	14.5	25	18.0	24	11.5	34	14.4	
2016	294	15.6	109	17.4	5	3.6	32	15.3	36	15.3	
2017	300	16.0	95	15.2	11	7.9	43	20.6	37	15.7	
2018	358	19.1	113	18.1	18	12.9	57	27.3	44	18.6	
2019	299	15.9	82	13.1	41	29.5	40	19.1	45	19.1	
Other antifungal usage, 14 days before AMB*	730	38.9	285	45.5	137	61.7	230	60.7	78	33.1	<.001*
Other antifungal usage, concomitant AMB											<.001*
Azole	679	36.1	377	36.2	67	30.2	126	33.2	104	44.1	

Flucytosine	56	3.0	20	1.9	5	2.3	15	4.0	12	5.1	
Echinocandin	92	4.9	14	1.3	23	10.4	42	11.1	12	5.1	
Median real days of AMB use, [25th – 75th]	14 [7 - 21]		10 [6 - 15]		9 [5 - 16]		10 [6 - 16]		19 [12 - 30]		0.001**
Median AMB dosage, mg/kg [25th – 75th]											
Pediatrics	-		1 [0.9 – 1.0]		3.1 [3 - 4.2]		4.8 [4.5 – 5.0]		-		0.002**
Adults	-		0.8 [0.71 – 0.98]		3.2 [3.0 – 4.2]		4.6 [3.7 – 5.0]		-		0.002**

Legend: D-AMB, deoxycholate amphotericin B; L-AMB, liposomal amphotericin B; ABLC, lipid complex amphotericin B; HIV+, HIV-positive; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplant; AMB, amphotericin B; ICU, intensive care unit; mg/kg, milligram/kilogram. * Chi-square test; **ANOVA

Effectiveness

The overall success rate after AMB treatment was 63% (95% CI 60 – 65). Rates of partial/complete response, disease progression or failure, and mortality are summarized in Table 3. Disease progression or failure was observed in 2% (95% CI 2 – 3.6) of patients treated with amphotericin B. The overall in-hospital mortality rate was 33% (95% CI 31.8 – 36.2). ABLC proved to be more effective among the formulations with 53% (95% CI 46.1 – 59.9) within complete response (P=0.039) and D-AMB with 18.7% (95% CI 15.7 – 22.0) of partial response (P<.001). The analyses also showed a limitrophe P value comparing mortality among formulations.

Table 3. Effectiveness of different amphotericin B formulations.

Comprehensive assessment of effectiveness at the end of treatment, n (%); 95% CI	Overall response AMB n of patients (%) [95% CI]	D-AMB		L-AMB		ABLC		P value
		n of patients (%)	95% CI	n of patients (%)	95% CI	n of patients (%)	95% CI	
Complete response with cure or improved hospital discharge	949 (51%) [49.3 – 53.9]	269 (42.9)	39.0 – 46.9	63 (45.3)	36.9 – 53.9	111 (53)	46.1 – 59.9	0.039*
Partial response with improved hospital discharge	212 (11%) [10.1 – 13.1]	117 (18.7)	15.7 – 22.0	12 (8.6)	4.7 – 14.9	17 (8.1)	4.9 – 12.9	<.001*
Disease progression or failure	51 (2%) [2 – 3.6]	10 (1.6)	0.8 – 3.0	4 (2.9)	0.9 – 7.0	7 (3.3)	1.4 – 7.0	0.262*
Death	639 (34%) [31.8 – 36.2]	202 (32.3)	28.6 – 36.1	59 (42.4)	34.2 – 51.1	66 (31.6)	25.4 – 38.4	0.056*

Legend: * Chi-square test

Subgroup analyzes were conducted to assess the effectiveness and impact of each and between AMB formulations. The overall success rates of ABLC, L-AMB and D-AMB are shown in Figures 2, 3 and 4, respectively. For the ABLC group it varied numerically among patient profiles, with higher rates for SOT (72.2% [46-89]) and lower for HIV+ (45.5% [18-75]). Overall success rates were numerically higher among patients with a probable or a proven diagnosis (65% [95% CI 48-79] and 62.5% [95% CI 50–73], respectively), compared with those who had a possible diagnosis (58.8% [95% CI 48–68]). Stratification according to combination therapy did not show statistical significance when ABLC was used associated with another antifungal drug. Regarding to the causative organism, overall success reached minimum rates of 50% with *Fusarium* spp. to 90.9% with a mix of other agents when treated with ABLC in monotherapy. From a statistical perspective, the overall success rate was progressively higher for those who received treatment for a longer duration, ≥4 weeks

(88.2% [95% CI 62–98]) compared with <1 week (43.5% [95% CI 31–57]), including the intermediates 1 to 2 weeks and 2 to 4 week's treatment duration (60% and 73.3%, respectively) (P<0.001).

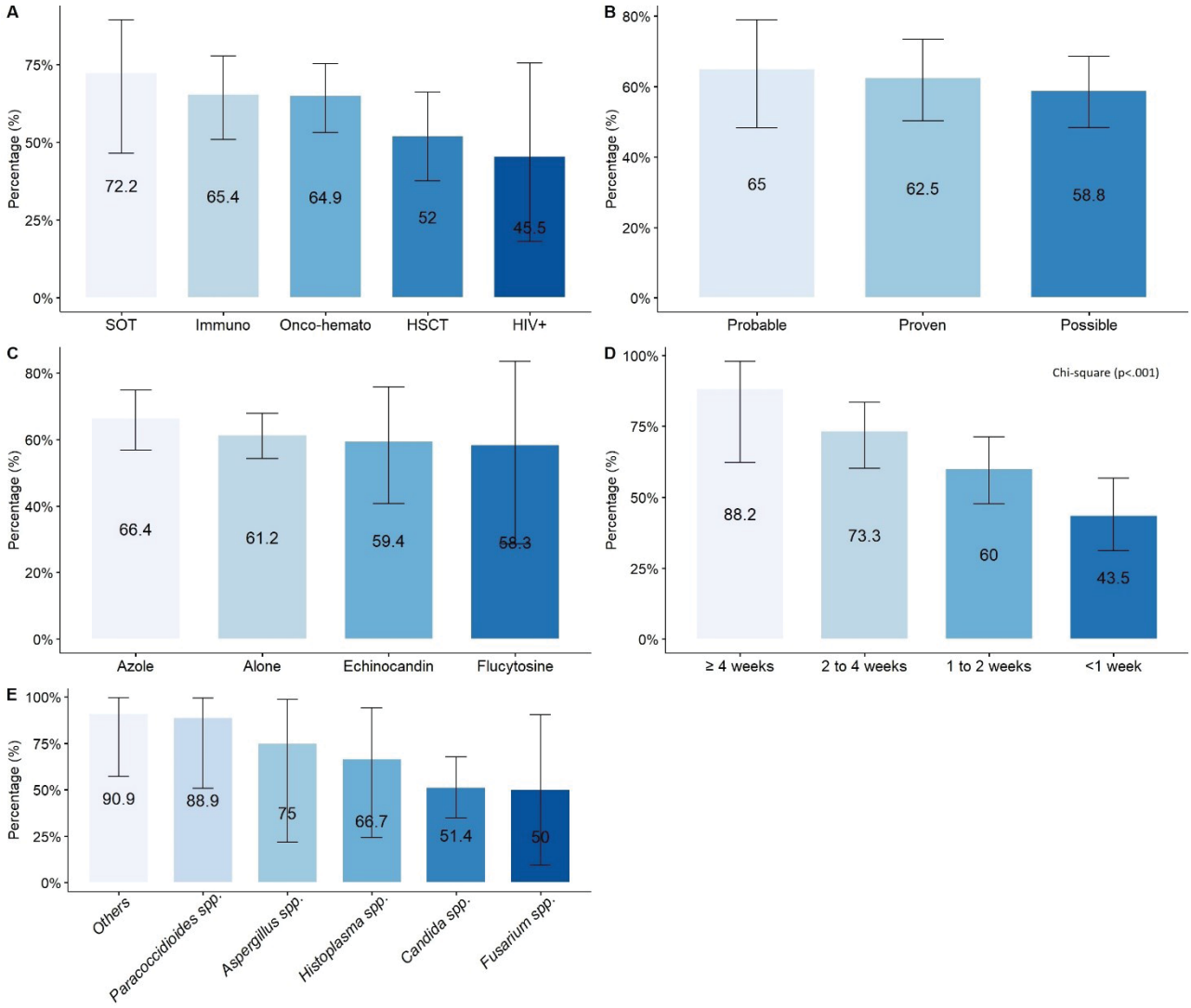


Figure 2. Amphotericin B lipid complex (ABLC) in monotherapy overall success rates (proportion of patients with complete or partial response) at the end of treatment according to A. patient profile, B. diagnostic certainty, C. combined therapy, D. treatment duration, and E. etiologic agent isolated in culture. P values indicate significant differences between treatment groups; error bars represent asymptotic 95% confidence intervals.

In the same line, the overall success rate of D-AMB was progressively higher for those who received treatment for a longer duration, reaching 71.9% when used for more than two weeks (P<0.001; 95% CI 65–78). For the conventional formulation a statistical significance was also seen on the subgroup analyses of patient profile and etiologic agent's (P<0.001; 95% and P=0.017, respectively).

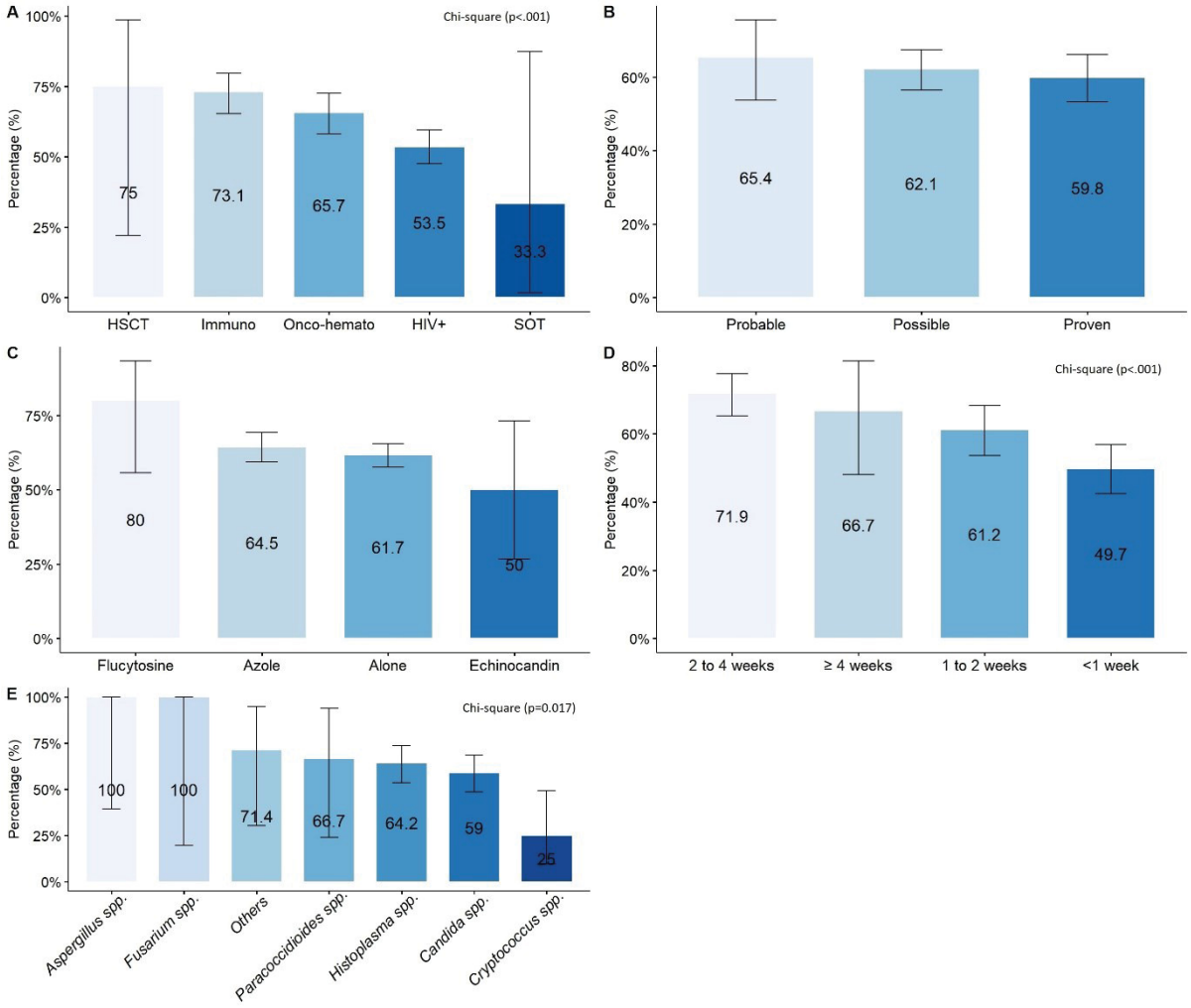


Figure 3. Amphotericin B deoxycholate (D-AMB) in monotherapy overall success rates (proportion of patients with complete or partial response) at the end of treatment according to A. patient profile, B. diagnostic certainty, C. combined therapy, D. treatment duration, and E. etiologic agent isolated in culture. P values indicate significant differences between treatment groups; error bars represent asymptotic 95% confidence intervals.

For L-AMB, additionally to the other formulations, significant result among diagnosis certainty were also observed (P=0.009). The comparison among the three formulations is represented in Figure 5.

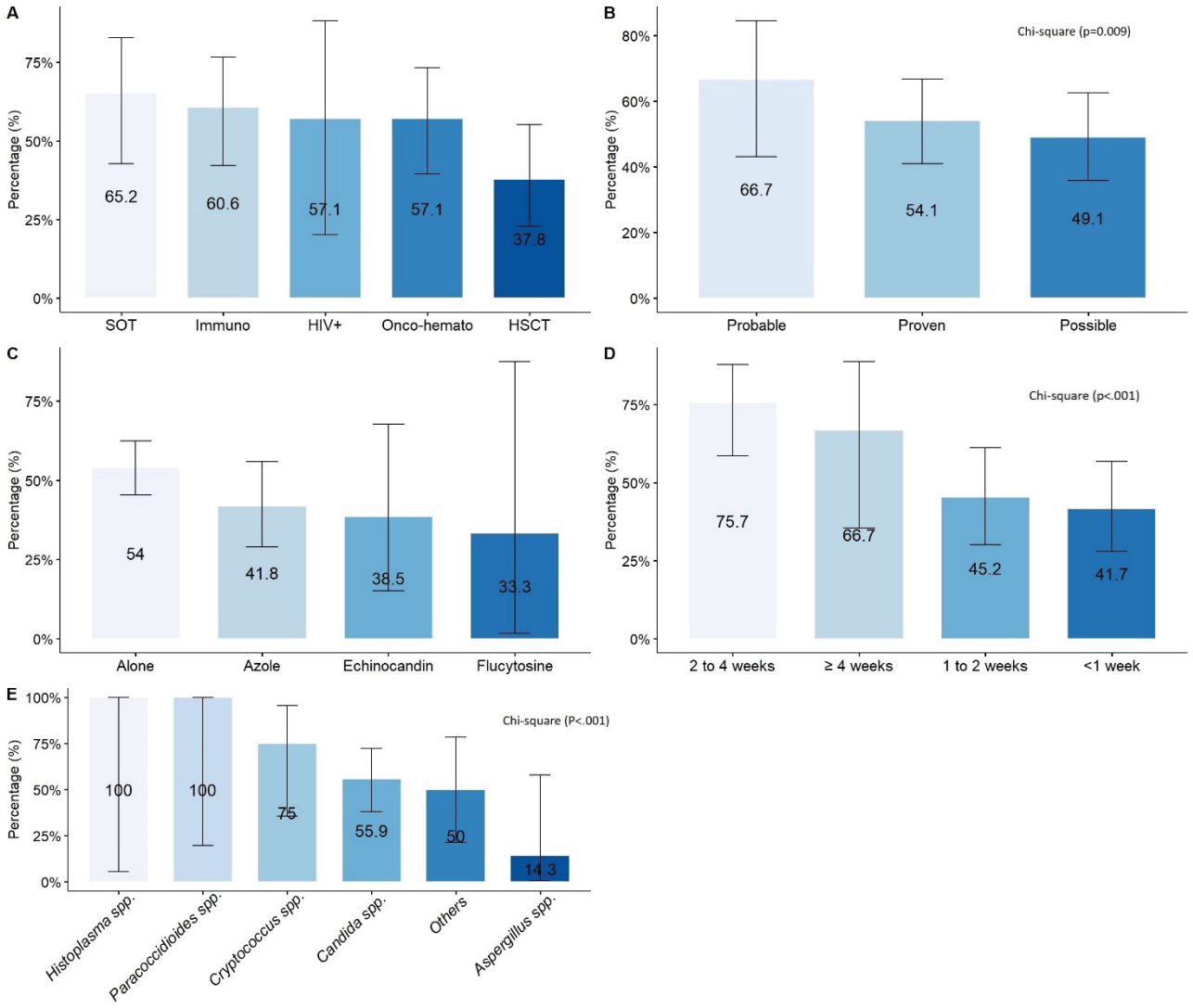


Figure 4. Amphotericin B liposomal (L-AMB) in monotherapy overall success rates (proportion of patients with complete or partial response) at the end of treatment according to A. patient profile, B. diagnostic certainty, C. combined therapy, D. treatment duration, and E. etiologic agent isolated in culture. P values indicate significant differences between treatment groups; error bars represent asymptotic 95% confidence intervals.

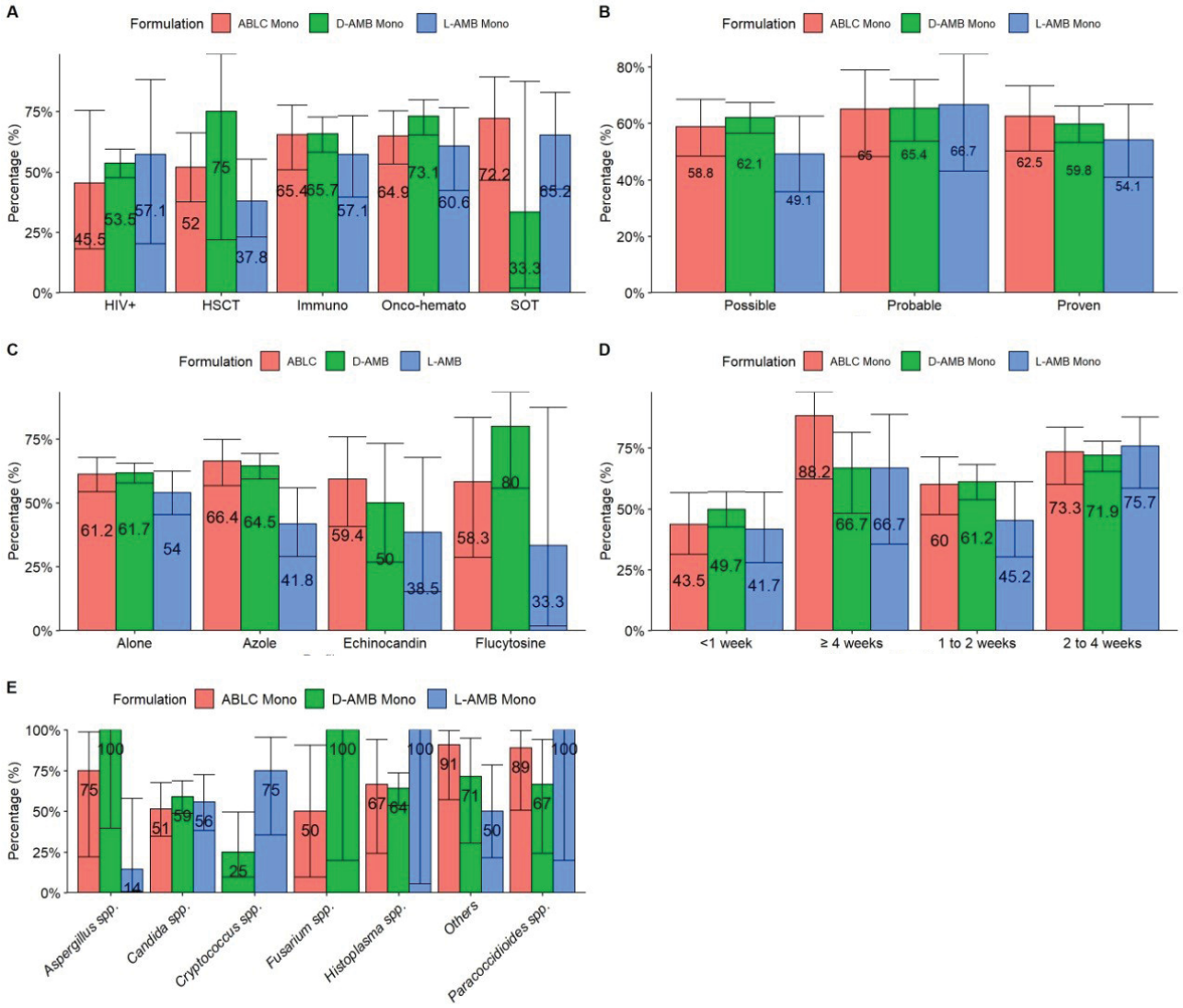


Figure 5. Comparison of overall success rates among amphotericin B formulation (proportion of patients with complete or partial response) at the end of treatment according to A. patient profile, B. diagnostic certainty, C. combined therapy, D. treatment duration, and E. etiologic agent isolated in culture. Error bars represent asymptotic 95% confidence intervals.

Legend: Mono, monotherapy.

Tolerability and safety

The overall tolerability profile of AMB formulations is summarized in Table 4. In total, acute IRSE was observed in 446 (23.7%) patients. The lipid complex represents 29.4% of them. In most cases fever and tremors or chills occurred, for both, pediatrics, and adults. For children, local pain during infusion was the acute reaction that presented statistical significance between AMB formulations (P=0.032). For adults, fever, rash/ itching, tremors/ chills, phlebitis, nausea/ vomiting,

and tachycardia showed significance. Nine patients, two (2.0%) pediatrics and two (0.8%) adults had mild or moderate IRSE with the suspension of the infusion for some period but with no discontinuation of treatment. Severe cases that had to discontinue therapy as a result of IRSE added nineteen cases (4.2%).

A very high percentage of patients in concomitant use of other potentially toxic drugs was also observed, with 99% and 89% for pediatrics and adults, respectively. The main drugs used in the same period of treatment with AMB were vancomycin, sulfamethoxazole + trimethoprim, acyclovir or ganciclovir, and diuretics.

Regarding safety, of the 1879 patients, 637 (33.9%) showed some alteration in creatinine levels during AMB exposure, 70 (11%) with the demand of dialysis. When stratified by formulation, 351 (55.1%) belonged to D-AMB group, 37 (10.5%) went through dialysis; 59 (9.3%) were from L-AMB group, with 5 (8.5%) dialysis needed; and 121 (19%) from ABLC group, 13 (10.7%) with the demand of dialysis (data not showed). Despite this, of the totality of patients under AMB treatment, 89 (4.7%) had to interrupt or discontinue the drug within the first 14 days of therapy due to renal dysfunction or nephrotoxicity. From this, 55 (61.8%) patients were under D-AMB treatment, 5 (5.6%) from L-AMB, and 19 (21.3%) from ABLC group. The last one is represented by 4 pediatrics and 15 adults (Table 4).

About hydroelectrolytic disorder, a total of 1115 (59.3%) patients needed potassium replacement after hypokalemia induced by AMB; 608 (54.5%) from D-AMB, 120 (10.8%) from L-AMB, and 227 (20.4%) from ABLC group. Interruption or discontinuation by hydroelectrolytic disorder summed up 6 (0.32%) patients. One thousand thirty-nine (55.3%) patients received a transfusion of hemocomponents soon after the start or during the AMB therapy period: 548 (54.5%) from D-AMB, 129 (10.8%) from L-AMB, and 241 (20.4%) from ABLC group. However, only 2 (0.1%) had to interrupt/discontinue by a blood disorder or hematological toxicity. Altered electrocardiograms were observed in 106 (5.6%) patients during exposure to AMB: D-AMB (47, 44.3%), L-AMB (10, 9.4%), ABLC (24, 22.6%) and 39 (2.1%) after therapy: D-AMB (20, 51.3%), L-AMB (0), ABLC (11, 28.2%), without any interruption or discontinuation within the first 14 days of therapy due to cardiotoxicity (data not showed). Sixty (17.2%) deaths were also reported during the first two weeks of AMB treatment. None were directly related to the polyene drug.

Table 4. Tolerability and safety profile of amphotericin B formulations.

			PEDIATRICS n= 578							ADULTS n= 1301						
	Total* n= 1879	%	D-AMB n= 313 n of events	%	L-AMB n= 48 n of events	%	ABLC n= 124 n of events	%	P value	D-AMB n= 729 n of events	%	L-AMB n= 165 n of events	%	ABLC n= 255 n of events	%	P value*
Acute IRSE considered to be drug related, n of patients	**446**	23.7	48	15.3	8	16.7	40	32.3	<.001	128	17.6	45	27.3	91	35.7	<.001
Fever	211	47.3	25	11.8	3	1.4	28	13.3	0.227	44	20.9	17	8.1	53	25.1	0.008
Rash/ itching	51	11.4	16	31.4	1	2.0	6	11.8	0.170	7	13.7	6	11.8	2	3.9	0.065
Tremor/ chills	144	32.3	24	16.7	1	0.7	18	12.5	0.180	25	17.4	6	4.2	40	27.8	<.001
Local pain during infusion	32	7.2	2	6.3	2	6.3	1	3.1	0.032	9	28.1	2	6.3	9	28.1	0.703
Phlebitis	39	8.7	0	0.0	0	0.0	0	0.0	X	31	79.5	1	2.6	2	5.1	<.001
Nausea/ vomiting	106	23.8	10	9.4	0	0.0	2	1.9	0.135	37	34.9	12	11.3	15	14.2	0.008
Migraine	40	9.0	2	5.0	0	0.0	0	0.0	0.447	14	35.0	4	10.0	8	20.0	0.385
Tachycardia	71	15.9	8	11.3	2	2.8	3	4.2	0.065	6	8.5	16	22.5	21	29.6	<.001
Other	133	29.8	18	13.5	4	3.0	11	8.3	0.769	35	26.3	7	5.3	29	21.8	0.264
Mild/Moderate with suspension but no discontinuation	12	2.7	5	41.7	0	0.0	2	16.7	0.277	7	58.3	0	0.0	2	16.7	0.408
Severe/discontinuation	22	4.9	5	22.7	0	0.0	1	4.5	0.452	5	22.7	1	4.5	4	18.2	0.572
Concomitant use of any other potentially toxic drug, n of patients	**1668**	88.8	250	79.9	41	85.4	123	99.2	<.001	662	90.8	148	89.7	227	89.0	<.001
Vancomycin	586	35.1	162	51.8	17	35.4	72	58.1	0.039	117	16.0	52	31.5	81	31.8	<.001
Polymyxin B or E	226	13.5	9	2.9	13	27.1	18	14.5	<.001	50	6.9	58	35.2	45	17.6	<.001
Gentamicin/ Amikacin	174	10.4	56	17.9	9	18.8	25	20.2	0.810	22	3.0	22	13.3	14	5.5	<.001
Sulfamethoxazole + trimethoprim	984	59.0	91	29.1	18	37.5	61	49.2	<.001	510	70.0	72	43.6	121	47.5	<.001
Imipenem	154	9.2	2	0.6	0	0.0	5	4.0	<.001	110	15.1	0	0.0	7	2.7	<.001
NSAIDs	319	19.1	7	2.2	7	14.6	11	8.9	<.001	174	23.9	49	29.7	40	15.7	<.001
Acyclovir/ Ganciclovir	537	32.2	24	7.7	13	27.1	53	42.7	<.001	186	25.5	76	46.1	109	42.7	<.001
Cyclosporine	110	6.6	4	1.3	9	18.8	30	24.2	<.001	1	0.1	24	14.5	25	9.8	<.001
Tacrolimus	59	3.5	1	0.3	1	2.1	8	6.5	<.001	0	0.0	18	10.9	19	7.5	<.001
Foscarnet	10	0.6	0	0.0	1	2.1	2	1.6	0.040	1	0.1	3	1.8	1	0.4	0.007
Tenofovir	278	16.7	1	0.3	0	0.0	0	0.0	0.499	218	29.9	10	6.1	24	9.4	<.001
ACE	115	6.9	12	3.8	3	6.3	20	16.1	<.001	20	2.7	8	4.8	23	9.0	<.001
Diuretics	639	38.3	118	37.7	19	39.6	74	59.7	<.001	156	21.4	65	39.4	112	43.9	<.001
Chemotherapy	140	8.4	16	5.1	8	16.7	34	27.4	<.001	6	0.8	11	6.7	36	14.1	<.001
Interruption or Discontinuation ≤ 14 days by, n of patients	***349***	18.6	76	24.3	5	10.4	25	20.2	-	141	19.3	23	13.9	48	18.8	-
Renal disfunction or nephrotoxicity	89	25.5	7	7.9	0	0.0	4	4.5	0.146	48	53.9	5	5.6	15	16.9	0.704
Hydroelectrolytic disorders	6	1.7	1	16.7	0	0.0	1	16.7	0.271	1	16.7	0	0.0	1	16.7	0.057
Blood disorders or hematological toxicity	2	0.6	0	0.0	0	0.0	0	0.0	-	1	50.0	0	0.0	1	50.0	0.752
Adverse Drug Reaction	24	6.9	5	20.8	0	0.0	2	8.3	0.062	6	25.0	1	4.2	4	16.7	0.247
Death	60	17.2	8	13.3	1	1.7	7	11.7	0.225	26	43.3	5	8.3	10	16.7	0.659
Other reason	132	37.8	48	36.4	3	2.3	11	8.3	0.222	36	27.3	10	7.6	13	9.8	0.218
Not informed	23	6.6	5	21.7	1	4.3	0	0.0	0.164	10	43.5	2	8.7	5	21.7	0.189

Legend: D-AMB, deoxycholate amphotericin B; L-AMB, liposomal amphotericin B; ABLC, lipid complex amphotericin B. * Chi-square test or Fisher correction.

Clinical management involved in the administration of Amphotericin B

Of the total number of individuals on AMB therapy, 705 (37.5%) received some medication to prevent infusion reactions. Of the patients who, despite having been reported IRSE, continued treatment without receiving any premedication before the subsequent doses, counted up 143 (32.1%). Regarding the premedication used, the main ones were antihistamines and corticosteroids, with 379 (53.8%) and 325 (46.1%) prescriptions, respectively. Also, 320 (45.4%) of patients received dipyrone, 128 (18.2%) paracetamol, 77 (11%) other drugs, and 71 (10%) patients received potassium as premedication before AMB infusion. Half of the patients (952, 50.6%) received some hydration with at least one liter of saline solution (NaCl 0.9%) in 24 hours, however, 27.3% of them irregularly. The time of intravenous infusion of AMB was 4 hours or more for 1021 (54.3%) of the individuals. Three hundred sixty-one (19.2%) patients received the infusion in a period of 2 hours and 111 (5.9%) in 1, 3, or 6 hours. In 397 (21.1%) prescriptions there was no information on the infusion time at which AMB should be administered. More detailed data about each formulation can be seen in Figure 3.

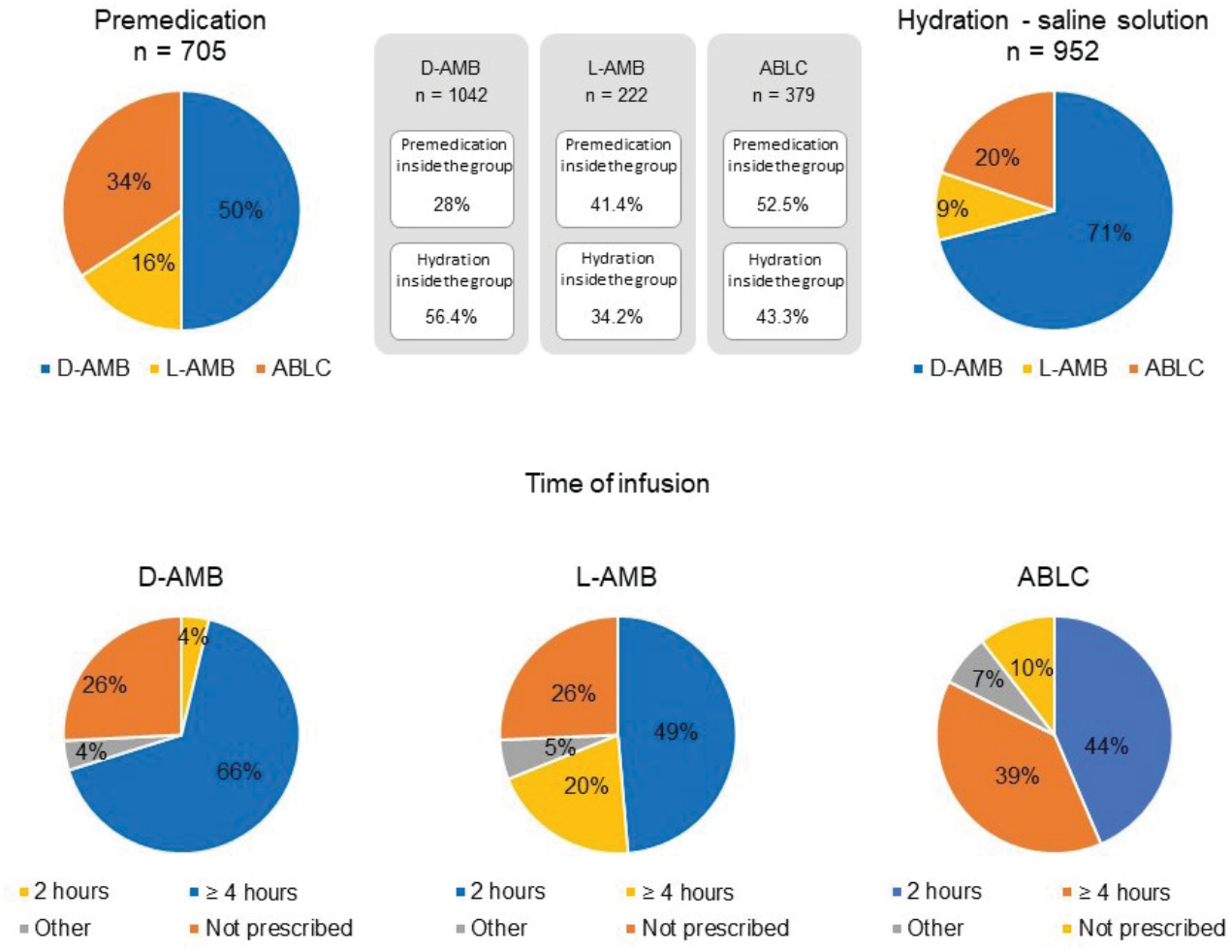


Figure 6. Clinical management for the administration of different amphotericin B formulations.

Legend: D-AMB, deoxycholate amphotericin B; L-AMB, liposomal amphotericin B; ABLC, lipid complex amphotericin B.

DISCUSSION

This retrospective analysis at ten Brazilian centers, including pediatric and adult patients, provides real evidence that intravenously administered amphotericin B lipid complex is effective against IFIs when used as empirical therapy or driven by a probable/proven diagnosis.

The AMB overall success rates observed are broadly comparable to those of other studies compiled in meta-analyses, which adds to the strength of evidence. [SAFDAR, 2010][HAMIL, 2013][TONIN, 2017]. In our study, ABLC proved to be more effective among formulations with 53% (95% CI 46.1 – 59.9) exclusive of complete response (P=0.039). Sidhu et al. (2018) also described a successful treatment achieved in 73.0% of ABLC patients and 68.8% of L-AMB patients (P=0.700). Moghnieh (2016) reported an overall response rate of 71%.

Stratification of the findings by treatment duration indicated that all formulations treatment was statistically significance more effective when continued for longer than 1 week. This is a potentially important finding which emphasizes the consequence of treating high-risk patients with IFIs for a minimum duration of 14 days, as suggested in most recent guidelines. [PAPPAS, 2016] [HOENELIG, 2018] [CORNELY, 2019] [CHEN, 2020] [THOMPSON, 2020]

Our analyses also showed that ABLC was well tolerated and safe. Despite the higher incidence of IRSE among formulations, very few interruption or discontinuation in treatment were seen. A descriptive study of 28 patients with severe (acute and chronic) forms of paracoccidioidomycosis treated initially with ABLC showed as common side effects hypomagnesaemia, anemia, and chills. Acute renal failure occurred in three patients (11%), but there were no treatment interruptions. [PEÇANHA, 2016] In another study, infusion-related reactions were observed in 36% of the patients, with a decrease in the incidence of these reactions upon using combination of premedication drugs [MOGHNIEH, 2016].

Overall, the data add to the growing body of evidence demonstrating the effectiveness, tolerability, and safety of ABLC, L-AMB and D-AMB for the treatment of patients with invasive fungal

infections; however, it is difficult to compare this real-life study directly with others because of differences in the patient populations and in the way that AMB treatment was evaluated. In addition, more than 70% of trials are known to have been industry-funded or reported a conflict of interest. [TONIN, 2017].

For example, studies in AMB toxicity provided diverse results of differences between LFABs. Hachem et al. (2008) found no difference in nephrotoxicity between L-AMB and ABLC, even though the analysis was not adjusted by any covariates, particularly baseline serum creatinine levels. Falci et al. (2015) did not directly compare the two lipid formulations. The authors found in a multivariate analysis that L-AMB had a protective effect on nephrotoxicity using D-AMB as a reference. The same conclusion was not extended to ABLC. An American study that compared both formulations directly using a multivariate analysis observed a higher chance to develop nephrotoxicity in the ABLC group in comparison to L-AMB with no statistically significant differences in the outcomes of new on-set dialysis, length of hospital stay, or mortality between them. [WADE, 2013]

We couldn't see significant difference between formulations on mortality, besides a limitrophe value was identified (P=0.056). Johansen and Gøtzsche (2014) found that lipid-based amphotericin B was not more effective than conventional amphotericin B on mortality.

The strengths of this study are that it included a large patient population and that it provides real-world evidence of AMB effectiveness, tolerability, and safety in current clinical practice. Limitations of the study consist of its retrospective design; the impossibility of out-hospital follow-up may have contributed to the progress of effectiveness or a lack of reassessment following treatment. Also, the small patient numbers included in some subgroups of effectiveness may have limited the statistical analyses.

CONCLUSION

ABLC is effective and well-tolerated in the treatment of systemic fungal infections and remains a valuable therapeutic option in a variety of patients due to its broad antifungal spectrum and rarity of resistance. The lipid formulation present similar rates of treatment responses and safety outcomes, with no statistically significant differences regarding associated toxicity. A minimum of

two weeks of treatment should be prioritized. Standardization and improvement of clinical management during AMB administration is necessary to minimize harmful effects and avoid toxicity.

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4 CONSIDERAÇÕES FINAIS

Em 60 anos desde sua comercialização, a anfotericina B permanece padrão ouro para o tratamento de infecções fúngicas invasivas. As formulações lipídicas foram desenvolvidas para melhorar a tolerabilidade, com um espectro de atividade semelhante e um perfil de segurança mais favorável que a formulação convencional. Contudo, apresentam características farmacológicas distintas que devem ser levadas em consideração. Estudos multicêntricos comparativos são fundamentais para que as formulações lipídicas se tornem amplamente difundidas a um custo menor a fim de garantir que os pacientes se beneficiem da terapia e os profissionais tenham segurança de uso em sua prática clínica.

4.1 RECOMENDAÇÕES PARA TRABALHOS FUTUROS

A partir do robusto banco de dados gerado, demais estudos já estão em andamento no intuito de abordar mais sobre os aspectos epidemiológicos relacionados às infecções fúngicas invasivas e o perfil de segurança relacionado ao uso da AMB.

O encontro *Brazilian Meeting of Histoplasmosis*, realizado em maio de 2022 em Porto Alegre - RS, resultou em um artigo, já aceito na PLOS Neglected Tropical Diseases, que conta com dados do presente estudo multicêntrico.

A partir do levantamento desses dados, outro estudo está sendo elaborado, intitulado “Snapshot of amphotericin B use and its response in disseminated histoplasmosis: the Brazilian reality”.

Também, outro estudo está em fase de conclusão intitulado “Acute infusion-related side effects of amphotericin B lipid complex (ABLC) in onco-hematological patients: real-world data at a southern Brazilian reference center”.

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ANEXOS

Código identificador: _____ **(ver dicionário de termos para correto preenchimento)**

1. **Setor de Internamento:**

☐ Infectologia
☐ Hematologia/TMO/TCTH
☐ Pediatria
☐ UTI
☐ Outro: _____

2. **Dados demográficos:**

Sexo: ☐ M ☐ F Idade: ____ anos Peso: ____ Kg

3. **Doenças de base:**

☐ DM
☐ HAS
☐ HIV
☐ Hepatopatia crônica
☐ Nefropatia
☐ Neoplasia/Doença hematológica:
Qual? _____
☐ Outras condições associadas: _____

4. **Formulação de anfotericina B utilizada:**

☐ Desoxicolato (Anforicin B®, Funtex B® e Unianf®)
☐ Lipossomal (Ambisome®)
☐ Complexo lipídico (Abelcet®)
☐ Iniciou com uma formulação e foi alterada para outra – qual? _____

5. **Durante os <u>14 dias antes</u> de iniciar anfotericina B, o paciente estava em uso de:**
***(Se concomitante ao tratamento com anfotericina B, assinale também o segundo quadrado)**

☐ ☐ Vancomicina
☐ ☐ Polimixina B
☐ ☐ Gentamicina/Amicacina
☐ ☐ Aciclovir/Ganciclovir
☐ ☐ Ciclosporina
☐ ☐ Tacrolimus
☐ ☐ Imipenem
☐ ☐ AINEs
☐ ☐ Foscarnet
☐ ☐ Indinavir
☐ ☐ Tenofovir
☐ ☐ iECA
☐ ☐ Diuréticos
☐ ☐ Quimioterapia
☐ ☐ Sulfa+Trimetoprim (Bactrim®)

6. **Pré-medicação para o uso de Anfotericina B:**

☐ Sim ☐ Não

7. **Qual pré-medicação:**

☐ Dipirona ☐ Difenidramina ☐ Corticoide ☐ Outra: Qual? _____

8. **Reações observadas durante/logo após administração de Anfotericina B:**

☐ Febre
☐ *Rash* cutâneo
☐ Tremor
☐ Dor local na infusão
☐ Flebite
☐ Náusea/Vômito
☐ Cefaleia
☐ Outra: Qual? _____

9. **Data de início de AnfoB**: ____/____/_____ **Data de término de AnfoB:** ____/____/_____

Dose (mg/dia): _____ (se alteração na dose indicar: _____)
Tempo de infusão (horas): _____
Reposição salina (≥ 1 litro/dia): ☐ SIM ☐ NÃO ☐ IRREGULAR
O tratamento com anfotericina B foi contínuo? ☐ SIM ☐ NÃO
Se NÃO, porque foi interrompido ou descontinuado:
_____
_____

Modelo de Ficha Clínica • Coleta de Dados
Estudo Multicêntrico

10. Parâmetros clínicos relevantes para investigação de toxicidade:

	Baseline (Internamento)	Dia 1 AnfoB	Metade Tratamento	Último dia AnfoB
Creatinina (mg/dL)				
Sódio (mEq/L)				
Potássio (mEq/L)				
Magnésio (mEq/L)				
Hemoglobina (g/dL)				
Leucócitos ($10^3/\mu L$)				
Neutrófilo segmentado ($10^3/\mu L$)				
Plaquetas (unidades/μL)				

11. Se Netropênico: Temperatura apresentou-se alterada na vigência de neutropenia (T ≥ 38°C)? ☐ SIM ☐ NÃO

Eletrocardiograma	Principais achados
Controle antes Anfotericina B	
Durante tratamento?	
Após Anfotericina B	

12. Diálise associada ao uso de Anfotericina B? ☐ SIM ☐ NÃO
13. Uso de granulócitos antes de Anfotericina B? ☐ SIM ☐ NÃO
14. Uso de granulócitos depois de Anfotericina B? ☐ SIM ☐ NÃO
15. Uso de eritropoietina (EPO) antes de Anfotericina B? ☐ SIM ☐ NÃO
16. Uso de eritropoietina (EPO) depois de Anfotericina B? ☐ SIM ☐ NÃO
17. Transfusão de hemocomponentes (concentrado de hemácias, sangue total, plaquetas, plasma fresco, crioprecipitado) após o início de Anfotericina B? ☐ SIM ☐ NÃO
18. Reposição de eletrólitos por hipocalemia (hipopotassemia)? ☐ SIM ☐ NÃO

19. Doença fúngica (EORTC/MSG):

☐ Possível ☐ Provável ☐ Comprovada **Qual doença?**
_____

20. Diagnóstico (poderá ser assinalada mais de uma alternativa):

☐ Micológico direto
☐ Cultura – Agente etiológico: _____
☐ Histopatológico
☐ Sorologia/Biomarcadores – Qual? _____
☐ Exame de imagem
☐ Teste rápido

21. Doença fúngica foi diagnosticada antes da prescrição de Anfotericina B? ☐ SIM ☐ NÃO

Sob qual critério? ☐ Profilático ☐ Empírico ☐ Guiado por diagnóstico EORTC/MSG

22. Desfecho:

☐ Alta Data: ____/____/_____ ☐ Óbito Data: ____/____/_____

23. Informações relevantes adicionais – Algum relato de toxicidade vinculado a Anfotericina B descrita no prontuário?

_____
_____

ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS BRASILEIROS.

Informações gerais:

Esta é uma pesquisa aplicada, de natureza observacional (estudo de coorte) e abordagem mista, do tipo documental. O estudo de coorte multicêntrico, retrospectivo, será conduzido em diversos hospitais terciários público-privados brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR).

Pretendemos, através dessa pesquisa, analisar dados obtidos em prontuários de pacientes internados, diagnosticados com infecção fúngica invasiva, seja de caráter endêmico ou oportunístico, e que foram tratados com diferentes formulações de anfotericina B: desoxicolato, lipossomal e complexo lipídico.

Deverão ser incluídos na coorte retrospectiva, prontuários de pacientes que preencham os seguintes critérios: **a) que tenham sido internados nos centros participantes pré-determinados; b) nos últimos seis anos (2014 – 2019); c) que tenham sido diagnosticados com algum tipo de infecção fúngica no mesmo período e; d) que tenham sido tratados com pelo menos uma das formulações de anfotericina B: desoxicolato, lipossomal e/ou complexo lipídico.**

- **Sugerimos que cada centro defina dois pesquisadores para participar do estudo (o pesquisador principal e um segundo a ser definido por ele para auxiliar nas coletas dos dados), os quais farão parte de publicações e trabalhos posteriores.**

- **As informações coletadas deverão ser retiradas a partir do prontuário médico do paciente internado. Por favor, não converse com o paciente ou seu familiar para obter mais informações.**

- **TODA a ficha clínica deverá ser preenchida. Ela será disponibilizada via formulário eletrônico. Pedimos que o campo CÓDIGO IDENTIFICADOR seja preenchido com bastante cautela para evitar possíveis erros de identificação. No centro coordenador (CHC/UFPR), serão avaliados todos os elementos em relação à consistência dos dados. Dados inconsistentes serão reenviados aos centros de origem para esclarecimento ou correção.**

***O prazo máximo para coleta e envio dos formulários será de doze (12) meses após a inclusão dos centros coparticipantes na Plataforma Brasil com a devida liberação do parecer ético.**

Em resumo, através desse estudo, será cabível a disponibilização a nível nacional e internacional, de novas informações acerca dos benefícios e qualidade terapêuticos dentre as diferentes formulações de Anfotericina B, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com diagnóstico de doença fúngica invasiva. Além do mais, o levantamento da efetividade, tolerabilidade e da segurança dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Definições importantes:

Infecção Fúngica Invasiva (IFI): Esse termo foi adotado para refletir com mais precisão o processo da doença causada por infecção fúngica e compreende três elementos principais representados pelos fatores do hospedeiro, manifestações clínicas e evidência micológica (última atualização do EORTC/MSG *Consensus Group* consta em De Pauw et al., 2008). O item 19 desse dicionário traz descritos tais elementos.

CÓDIGO IDENTIFICADOR: Para identificação de cada ficha, o código do paciente será composto de três componentes. Quatro primeiras letras identificarão o centro coparticipante (ex.: HCPR), seguido do ano da internação (ex.:HCPR2014) e do número que referencie o prontuário pesquisado utilizando sempre um zero "0" na frente e em número crescente (ex.: HCPR201401; HCPR201402; HCPR201403 etc..). Quando o ano mudar, a numeração deverá ser iniciada novamente (ex.: HCPR201501; HCPR201502 etc..) e assim por diante até fechar o ano de 2019.

GUIA PARA QUESTÕES ESPECÍFICAS:

1) SETOR DE INTERNAMENTO
Especifique em qual serviço o paciente permaneceu durante o tratamento com Anfotericina B. Se o paciente foi internado em uma unidade, porém foi transferido para um setor específico onde permaneceu para o tratamento, este deverá ser especificado.
TMO = Transplante de Medula Óssea
TCTH = Transplante de Células-Tronco Hematopoiética

2) DADOS DEMOGRÁFICOS
Informe o sexo, a idade do paciente e o peso em quilogramas (Kg) no momento da internação. Caso não conste no prontuário digite NI (não informado).

3) DOENÇAS DE BASE
Informe se o paciente apresentava alguma doença/condição prévia à internação.
DM = *Diabetes mellitus*
HAS = Hipertensão Arterial Sistêmica
HIV = Vírus da Imunodeficiência Humana

4) FORMULAÇÃO DE ANFOTERICINA B UTILIZADA
Assinale a formulação de anfotericina utilizada durante todo o tratamento. Caso o paciente tenha iniciado com uma formulação e depois tenha sido alterado para outra, especifique qual (ex: desoxicolato → complexo lipídico).

5) DURANTE OS 14 DIAS ANTES DE INICIAR ANFOTERICINA B ESTAVA EM USO DE
Assinale todos os medicamentos que o paciente tenha utilizado nos quatorze dias que antecederam o tratamento com anfotericina B. Se houve uso concomitante (ou seja, se foi mantido o medicamento durante o tratamento com anfotericina B, assinalar na segunda coluna no campo indicado).
AINEs = Anti-inflamatórios não esteroidais
iECA = Inibidores da enzima conversora de angiotensina

6) PRÉ-MEDICAÇÃO PARA O USO DE ANFOTERICINA B
Assinale SIM apenas se constar no prontuário que algum medicamento tenha sido expressamente prescrito como pré-medicação para anfotericina. Muitas vezes vem indicado como "*pré anfo-B*", "*fazer antes da dose de anfo-B*", "*administrar 30 min antes de anfo-B*" etc.

7) QUAL PRÉ-MEDICAÇÃO
Assinale um ou mais campos indicando o(s) medicamento(s) utilizado(s), referidos como pré-medicação.

8) REAÇÕES OBSERVADAS DURANTE/LOGO APÓS ADMINISTRAÇÃO DE ANFOTERICINA B:
Reporte se alguma reação adversa foi observada enquanto a anfotericina foi administrada ou logo após sua administração e que tenha sido registrada no prontuário vinculado ao seu uso.

9) NESSA ETAPA INDIQUE
- A data de início e término do tratamento com anfotericina B;
- Quantos miligramas (mg) por dia foi prescrito de anfotericina B para o paciente. Se houve mudança na dose, por favor, informe no campo indicado;
- O tempo de infusão em horas. Caso essa informação não conste na prescrição, digite NI (não informado);
- Se houve reposição com soro fisiológico (NaCl 0,9%) durante administração de anfotericina B;
- Se caso o tratamento tenha sido descontinuado justifique o motivo de tal decisão (intolerância ao medicamento, permuta de terapia, toxicidade etc..)

10) PARÂMETROS CLÍNICOS RELEVANTES PARA INVESTIGAÇÃO DE TOXICIDADE
Preencha o quadro com o máximo de informações a cerca dos exames solicitados. A primeira coluna refere-se ao primeiro exame realizado quando o paciente foi admitido no serviço. Caso no dia do internamento algum exame não tenha sido realizado pode ser considerado resultados até 48h após internamento. O mesmo serve para as próximas colunas: durante tratamento com a anfotericina B e ao seu término. O ideal é que os resultados sejam dos dias de início, meio e final do tratamento, podendo variar em 24h (para mais ou menos) caso algum resultado não seja encontrado na data exata. Com relação ao eletrocardiograma, indique (se for o caso) os principais achados do exame antes, durante e após uso de anfotericina B.

11) SE NEUTROPÊNICO: TEMPERATURA APRESENTOU-SE ALTERADA NA VIGÊNCIA DE NEUTROPENIA (T ≥ 38°C)?
Caso tenha sido identificado valores de neutrófilos inferiores a 500/μL, informe se a temperatura mostrou-se igual ou superior à 38ºC.

12) DIÁLISE ASSOCIADA AO USO DE ANFOTERICINA B
Informe se houve necessidade de diálise relacionada ao uso de anfotericina B.

13) USO DE GRANULÓCITOS ANTES DE ANFOTERICINA B
Informe se foi administrado granulócitos antes de iniciar o tratamento com anfotericina B.

14) USO DE GRANULÓCITOS DEPOIS DE ANFOTERICINA B
Informe se foi administrado granulócitos após o início do tratamento com anfotericina B.

15) USO DE ERITROPOETINA (EPO) ANTES DE ANFOTERICINA B
Informe se foi administrado EPO antes de iniciar o tratamento com anfotericina B.

16) USO DE ERITROPOETINA (EPO) ANTES DE ANFOTERICINA B
Informe se foi administrado EPO antes de iniciar o tratamento com anfotericina B.

17) TRANSFUSÃO DE HEMOCOMPONENTES (CONCENTRADO DE HEMÁCEAS, SANGUE TOTAL, PLASMA FRESCO, CRIOPRECIPITADO) APÓS INÍCIO DE ANFOTERICINA B?
Informe se o paciente recebeu transfusão de algum dos hemocomponentes indicados após ter sido iniciado o tratamento com anfotericina B.

18) REPOSIÇÃO DE ELETRÓLITOS POR HIPOCALEMIA (HIPOPOTASSEMIA)?
Assinale SIM se houve necessidade de reposição eletrolítica por diminuição dos níveis de K^+ (potássio) plasmático.

19) DOENÇA FÚNGICA (EORTC/MSG)

No campo "Qual doença" no nº 19 da ficha, indique o nome da doença fúngica provável ou comprovada.

Em 2002, um grupo de consenso da Organização Europeia de Pesquisa e Tratamento do Câncer/Grupo Cooperativo de Infecções Fúngicas Invasoras (EORTC) e do Instituto Nacional de Alergia e Doenças Infecciosas *Micoses Study Group* (MSG) publicou definições padrão para infecções fúngicas invasivas. Essas definições foram desenvolvidas para facilitar a identificação de grupos razoavelmente homogêneos de pacientes submetidos à pesquisa clínica e epidemiológica; ajudar a projetar ensaios clínicos para avaliar novas drogas e estratégias de manejo e; fomentar a comunicação entre pesquisadores internacionais. As definições atribuíram três (3) níveis de probabilidade ao diagnóstico de infecção fúngica invasiva que se desenvolve em pacientes imunocomprometidos com câncer e em receptores de transplante de células-tronco hematopoiéticas, intituladas "comprovada", "provável" e "possível" infecção fúngica invasiva (IFI).

Em 2008, em nova publicação revisada, o grupo reafirmou que as definições deveriam ser usadas apenas para auxiliar na pesquisa e que a integridade das definições originais com as classificações de IFI comprovada, provável e possível, seria preservada. Os critérios para comprovada e provável IFI foram modificados para refletir os avanços em testes indiretos, enquanto a categoria de possível IFI foi revisada para incluir apenas casos que são altamente prováveis de serem causados por uma etiologia fúngica, embora faltem evidências micológicas.

Critérios para IFI provada exceto para micoses endêmicas

Adaptado de De PB, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008 Jun 15;46(12):1813-21.(47)

Análise e espécime	Fungos filamentosos[a]	Leveduras[a]
Análise microscópica de material estéril	Exame histopatológico, citopatológico ou microscopia direta de material[b] adquirido através de aspirado por agulha ou biópsia onde são visualizadas hifas ou formas leveduriformes acompanhado de evidência de dano tecidual associado.	Exame histopatológico, citopatológico ou microscopia direta de material[b] adquirido através de aspirado por agulha ou biópsia do sítio normalmente estéril (outro além de membrana mucosa) demonstrando células leveduriformes – ex: espécies de *Cryptococcus sp* apresentadas como leveduras encapsuladas em brotamento ou espécies de *Candida* apresentadas como pseudohifas ou hifas[c].
Cultura de material estéril	Isolamento de fungo filamentoso ou "levedura negra" através de cultura de material adquirido em de procedimento estéril, do sítio normalmente estéril e sítio clinico ou radiológica anormal consistente com a doença infecciosa em processo. Excluindo-se lavado bronco alveolar, material de seios da face e urina.	Isolamento de levedura através de cultura de material adquirido em de procedimento estéril (incluindo dreno recém colocado – até 24h) de sítio normalmente estéril e de sítio clinico ou radiológica anormal consistente com a doença infecciosa em processo.
Cultura de sangue	Hemocultura com identificação de fungo filamentoso[d] (ex: espécies de *Fusarium*) no contexto de processo infeccioso compatível.	Hemocultura com levedura (ex: espécies de *Cryptococcus* ou *Candida*) ou fungo Leveduriformes (ex: espécies de *Trichosporon*)
Análise sorológica: LCR	Não aplicável	Antígeno criptocócico em LCR indica criptococose disseminada.

a Se a cultura está disponível a definição da IFI será baseada neste resultado; **b** Tecidos e células submetidas à estudos histopatológicos e citopatológicos devem ser corados com colorações específicas para fungo, para facilitar a inspeção das estruturas fúngicas; **c** Espécies de *Candida, Trichosporon* e forma leveduriforme de *Geotrichum* e *Blastoschizomyces capitatus* também podem formar pseudohifas ou hifas verdadeiras; **d** Isolamento de espécies de *Aspergillus* de hemoculturas, invariavelmente representam contaminação.

Critérios para IFI provável exceto para micoses endêmicas

Adaptado de De PB, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008 Jun 15;46(12):1813-21.(47)

Fatores do Hospedeiro[a]
História recente de neutropenia (<500 neutrofilos/mm3] por >10 dias) com relação temporal com o início da doença fúngica
Receptor de TCTH alogênico
Uso prolongado de corticoides (excluindo-se pacientes com aspergilose broncopulmonar crônica) em dose mínima equivalente de 0.3 mg/kg/dia de prednisona por 13 semanas.
Tratamento com outro imunossupressor de célula T como ciclosporina, bloqueador de TNF-α, anticorpos monoclonais específicos (como alemtuzumab), ou análogos de nucleosídeo nos últimos 90 dias.
Imunodeficiência hereditária grave (como doença granulomatosa crônica ou imunodeficiência combinada grave)
Critérios Clínicos[b]
o Doença fúngica do trato respiratório inferior
Presença de 1 dos 3 seguintes sinais na TC:
- Lesão (ou lesões) densa bem circunscrita com ou sem sinal do halo
- Sinal do crescente de ar
- Cavitação
o Traqueobronquite
Ulceração traqueobronqueal, nódulo, pseudomembrana, placa ou escara visualizada através de broncoscopia.
o Infecção Nasossinusal
Imagem que mostre sinusite além de pelo menos 1 dos 3 sinais que se seguem:
- Dor aguda localizada (inclui dor que irradia para o olho)
- Úlcera nasal com escara negra
- Extensão dos seios paranasais pelas barreiras ósseas, incluindo a órbita.
o Infecção no SNC
1 dos 2 sinais que se seguem:
- Lesões focais em imagem
- Captação meníngea em RNM ou TC
o Candidíase disseminada
Pelo menos 1 dos 2 seguintes achados após um episódio de candidemia ocorrido a menos de 2 semanas:
- Pequenos abcessos em forma de alvo no fígado ou baço
- Exsudato progressivo na retina em exame oftalmológico
Critério micológico
o Teste direto (citologia, microscopia direta, ou cultura)
Fungo filamentoso em escarro, lavado broncoalveolar, escovado brônquico, ou aspirado de seios da face, indicado por 1 dos seguintes:
- Presença de elementos fúngicos indicando um fungo
- Isolamento por cultura de um fungo filamentoso (ex: espécies de *Aspergillus, Fusarium,* Zygomycetes, ou *Scedosporium*)
o Testes indiretos (detecção de antígeno ou estruturas da parede celular)[c]
Aspergilose
Antígeno galactomanana detectado no plasma, soro, lavado broncoalveolar ou LCR
Outra doença invasiva fúngica além de criptococose e zigomicose
β-D-glucana detectado no soro

a Fatores clínicos não são sinônimos de fatores de risco e são características pelos quais indivíduos predispostos a IFI podem ser reconhecidos. A intenção é que sejam aplicados a pacientes em tratamento de doenças malignas e a receptores de TCTH alogênico e transplantes de órgão sólido; **b** Devem ser consistentes com os achados micológicos, se houver algum, e deve estar temporalmente relacionado ao episódio atual; **c** Esses testes são essencialmente aplicáveis a aspergilose e candidíase, e não são úteis no diagnóstico de infecções por espécies de *Cryptococcus* ou Zygomycetes (ex: *Rhizopus, Mucor,*ou *Absidia*). A detecção de ácido nucleico não foi incluída por não haverem ainda métodos validados ou padronizados. **TCTH** Transplante de células tronco hematopoéticas; **TC** Tomografia computadorizada; **RNM** Ressonância nuclear magnética; **LCR** Líquido cefalorraquidiano; **IFI** Infecção fúngica invasiva

NOTA A IFI provável requer a presença de um fator relacionado ao hospedeiro, um critério clínico e um critério micológico. Os casos que satisfazem os critérios para um fator hospedeiro e um critério clínico mas para o qual os critérios micológicos se ausentam consideram-se **IFI possível**.

Critérios para diagnóstico de micoses endêmicas

Adaptado de De PB, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008 Jun 15;46(12):1813-21.(47)

Diagnóstico e critérios
o Micose endêmica provada
Em um hospedeiro com doença consistente compatível com micose endêmica, um dos seguintes: - Recuperação em cultura de um espécime obtido do local afetado ou do sangue - Demonstração histopatológica ou microscópica direta de formas morfológicas apropriadas com característica de aparência verdadeiramente distinta de fungos dimórficos, como espéculos de espécies de *Coccidioides*, leveduras de brotamento de base larga de paredes espessas de *Blastomyces dermatitidis*, células de levedura de brotamento múltiplo de *Paracoccidioides brasiliensis* e, no caso de histoplasmose, presença de formas de levedura intracelular características em fagócito em esfregaço de sangue periférico ou em macrófagos teciduais. Para coccidioidomicose, demonstração de anticorpo coccidioidal no LCR, ou um aumento de 2 diluições medido em 2 amostras consecutivas de sangue testadas concorrentemente no contexto de um processo de doença infecciosa em curso Para paracoccidioidomicose, demonstração em 2 amostras consecutivas de soro de uma banda de precipitina para paracoccidioidina concomitantemente no contexto de um processo de doença infecciosa em curso
o Micose endêmica provável
Presença de um fator hospedeiro, incluindo, mas não se limitando àqueles especificados na tabela anterior, mais um quadro clínico consistente com micose endêmica e evidência micológica, como um teste de antígeno histoplasmático positivo resultante de urina, sangue ou LCR.

NOTA As micoses endêmicas incluem histoplasmose, blastomicose, coccidioidomicose, paracoccidioidomicose, esporotricose e infecção por *Penicillium marneffei*. Início dentro de 3 meses após a apresentação do quadro define uma infecção pulmonar primária. Não há categoria de possível micose endêmica, pois, nem os fatores do hospedeiro nem as características clínicas são suficientemente específicos; esses casos são considerados de valor muito limitado para incluir em estudos clínicos, estudos epidemiológicos ou avaliações de testes diagnósticos.

20) DIAGNÓSTICO

Assinale o(s) exame(s) que foram realizados para o diagnóstico da IFI.
Se a IFI for 'categoria provada', informe o agente etiológico resultante da cultura no campo indicado.

21) DOENÇA FÚNGICA FOI DIAGNOSTICADA ANTES DA PRESCRIÇÃO DE ANFOTERICINA B?

Assinale SIM apenas se a confirmação do diagnóstico da IFI ocorreu antes do início do tratamento com anfotericina B. Ao assinalar NÃO, assume-se que o tratamento começou profilaticamente, empiricamente, ou por suspeita, e que a confirmação ocorreu durante ou após tratamento. Indique também o critério utilizado.

22) DESFECHO

Informe se alta ou óbito e a data dos mesmos.

23) INFORMAÇÕES RELEVANTES ADICIONAIS

Nesse campo, o pesquisador é convidado a acrescentar alguma informação sobre toxicidade contida no prontuário que considere importante e que em campos anteriores não houve a oportunidade de descrever.

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S. Ascioglu, J. H. Rex, B. de Pauw, J. E. Bennett, J. Bille, F. Crokaert, D. W. Denning, J. P. Donnelly, J. E. Edwards, Z. Erjavec, D. Fiere, O. Lortholary, J. Maertens, J. F. Meis, T. F. Patterson, J. Ritter, D. Selleslag, P. M. Shah, D. A. Stevens, T. J. Walsh, Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases; **Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus**, *Clinical Infectious Diseases*, Volume 34, Issue 1, 1 January 2002, Pages 7–14, https://doi.org/10.1086/323335

Ben De Pauw B., Thomas J. Walsh, J. Peter Donnelly, David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, John E. Bennett; **Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group**, *Clinical Infectious Diseases*, Volume 46, Issue 12, 15 June 2008, Pages 1813–1821, https://doi.org/10.1086/588660

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: Flavio de Queiroz Telles Filho

Área Temática:

Versão: 9

CAAE: 87619218.5.1001.0096

Instituição Proponente: Hospital de Clínicas da Universidade Federal do Paraná

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.018.535

Apresentação do Projeto:

Trata-se de uma emenda para alterar o vínculo da instituição, a pedido da pesquisadora, na Plataforma Brasil, por equívoco no registro. Propõe-se a exclusão do centro participante GRUPO DE APOIO AO ADOLESCENTE E A CRIANÇA COM CÃNCER GRAACC e a inclusão do centro participante UNIFESP (60.453.032/0008-40) sob a coordenação da mesma pesquisadora, Fabianne Altruda de Moraes Costa Carlesse.

Objetivo da Pesquisa:

Sem relato de alterações em relação ao projeto original.

Avaliação dos Riscos e Benefícios:

Sem relato de alterações em relação ao projeto original.

Comentários e Considerações sobre a Pesquisa:

Emenda adequada

Considerações sobre os Termos de apresentação obrigatória:

Termos presentes

Conclusões ou Pendências e Lista de Inadequações:

Emenda aprovada

Endereço: Rua Gal. Carneiro, 181
Bairro: Alto da Glória **CEP:** 80.060-900
UF: PR **Município:** CURITIBA
Telefone: (41)3360-1041 **Fax:** (41)3360-1041 **E-mail:** cep@hc.ufpr.br

Considerações Finais a critério do CEP:

Diante do exposto, o Comitê de Ética em Pesquisa em Seres Humanos do HC-UFPR, de acordo com as atribuições definidas na Resolução CNS 466/2012 e na Norma Operacional Nº 001/2013 do CNS, manifesta -se pela aprovação da Emenda.

Solicitamos que sejam apresentados a este CEP, relatórios semestrais sobre o andamento da pesquisa, bem como informações relativas às modificações do protocolo, cancelamento, encerramento e destino dos conhecimentos obtidos. Manter os documentos da pesquisa arquivados.

É dever do CEP acompanhar o desenvolvimento dos projetos, por meio de relatórios semestrais dos pesquisadores e de outras estratégias de monitoramento, de acordo com o risco inerente à pesquisa.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1545583_E7.pdf	24/04/2020 17:36:14		Aceito
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Outros	CARTA_PARA_EMENDA_inclusao_centros.docx	29/08/2019 17:44:51	FRANCELISE BRIDI CAVASSIN	Aceito
Declaração de Pesquisadores	CARTA_EMENDA_PROJETO_ANFOTERICINA.doc	11/07/2019 11:47:48	Flavio de Queiroz Telles Filho	Aceito
Declaração de Instituição e Infraestrutura	Istituto_Infecto_ER_Jose_Vidal_Concordancia_de_Coparticipacao.jpg	21/05/2019 09:47:48	FRANCELISE BRIDI CAVASSIN	Aceito
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Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CURITIBA, 10 de Maio de 2020

Assinado por:
maria cristina sartor
(Coordenador(a))

HOSPITAL ERASTO GAERTNER - LIGA PARANAENSE DE COMBATE

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: Flavio de Queiroz Telles Filho

Área Temática:

Versão: 1

CAAE: 87619218.5.3004.0098

Instituição Proponente: Hospital Erasto Gaertner

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.134.745

Apresentação do Projeto:

As informações elencadas nos campos “Apresentação do Projeto”, “Objetivo da Pesquisa” e “Avaliação dos Riscos e Benefícios” foram retiradas do arquivo Informações Básicas da Pesquisa.

Trata-se uma pesquisa aplicada, de natureza observacional (estudo de coorte) e abordagem mista, do tipo documental. O estudo de coorte multicêntrico, retro e prospectivo, será conduzido em hospitais público-privados terciários brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR). Infecções fúngicas invasivas (IFIs) são de importância e interesse global. Pacientes com IFI grave são normalmente diagnosticados em hospitais públicos terciários e podem representar um desafio terapêutico para o sistema de saúde em países em desenvolvimento. Estima-se que, no mundo, mais de um bilhão de pessoas sofrem de uma infecção fúngica e que mais de 1,5 milhão de pessoas morrem a cada ano de uma infecção fúngica. No Brasil, poucas doenças fúngicas são notificadas ao Ministério da Saúde como coccidioidomicose, histoplasmose e paracoccidioidomicose, porém a carga de outras doenças fúngicas prevalentes no país é, ainda, desconhecida. As IFIs são difíceis de detectar e tratar e podem ser associadas à morbidade e mortalidade substanciais. O complexo lipídico de anfotericina B (ABELCET®) é fornecido pelo Ministério da Saúde brasileiro para o tratamento de pacientes com infecções fúngicas invasivas, internados em hospitais da rede SUS. Apesar do uso frequente desse medicamento, dados disponíveis que exponham sua eficácia, tolerabilidade e

segurança são escassos quando comparados a outras formulações disponíveis há mais tempo no mercado, como a anfotericina B-desoxicolato e a anfotericina B lipossomal. Através de um estudo de coorte multicêntrico, retro e prospectivo, que será conduzido em cinco hospitais terciários públicos brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR), será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade desse medicamento, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Objetivo da Pesquisa:

Objetivo Primário: Avaliar e comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B (desoxicolato, lipossomal e complexo lipídico) em hospitais terciários brasileiros.

Objetivo Secundário: Diferenciar, através de uma revisão de literatura, os aspectos farmacológicos das formulações de anfotericina B atualmente utilizadas para tratamento de infecções fúngicas invasivas;Coletar dados demográficos e epidemiológicos, fatores de risco e elementos farmacodinâmicos associados ao uso de anfotericina B obtidos em prontuários de pacientes diagnosticados com IFI e internados em hospitais da rede SUS;Analisar dados retrospectivos e prospectivos, obtidos em prontuários de pacientes internados no CHC/UFPR, diagnosticados com IFI e tratados com diferentes formulações de anfotericina B.Comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B nos dados que serão pesquisados;Relatar os benefícios terapêuticos do complexo lipídico de anfotericina B (ABELCET®) quando comparado ao tratamento convencional e/ou lipossomal.

Avaliação dos Riscos e Benefícios:

Riscos: Quebra de anonimato: os riscos serão minimizados através da não utilização de nomes ou siglas que possam, eventualmente, identificar os prontuários de pacientes que serão avaliados na pesquisa. O instrumento de coleta de dados utilizará variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da infecção fúngica invasiva, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos e serão coletados

exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo.

Benefícios: Através desse estudo, será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade de medicamentos antifúngicos, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Comentários e Considerações sobre a Pesquisa:

A presente emenda foi proposta para inclusão dos centros participantes, após aceite dos pesquisadores após convite de participação nesse estudo.:

1.Hospital de Clínicas de São Paulo (HC/SP)

2.Hospital de Doenças Tropicais (HDT-SES/GO)

3.Hospital Universitário Oswaldo Cruz da Universidade de Pernambuco (HUOC-UPE)

Como consta na primeira versão do projeto, os centros foram definidos após algumas reuniões que aconteceram em Brasília, na qual os pesquisadores foram convidados e puderam demonstrar interesse em participar do estudo multicêntrico. Nesse momento, mais três deles (Dr. Marcelo Magri; Dra. Cássia Godoy; Dr. Filipe Prohaska Batista) aceitaram participar.

Não foram identificados óbices éticos nesta emenda.

Considerações sobre os Termos de apresentação obrigatória:

Termos obrigatórios e considerações apresentados satisfatoriamente.

Conclusões ou Pendências e Lista de Inadequações:

O projeto está de acordo conforme itens acima analisados, sem lista de inadequações.

Considerações Finais a critério do CEP:

Continuação do Parecer: 4.134.745

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	CARTA_PARA_EMENDA_alteracao_UNIFESP.docx	24/04/2020 17:34:05	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_HUOP.pdf	13/03/2020 10:00:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_exclusao_Elaine.docx	05/12/2019 14:24:34	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	LISTA_DE_CENTROS_PARTICIPANTES_E_COPARTICIPANTES.docx	29/08/2019 17:45:29	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_centros.docx	29/08/2019 17:44:51	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_APRESENTACAO_E_JUSTIFICATIVA_PARA_EMENDA_AO_PROJETO.pdf	21/05/2019 09:40:48	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_ORIENTACAO.pdf	28/08/2018 13:58:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_COMPROMISSO.pdf	28/08/2018 13:58:05	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_CONFIDENCIALIDADE.pdf	28/08/2018 13:57:49	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_RESPONSABILIDADE.pdf	28/08/2018 13:57:06	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa_2.pdf	29/05/2018 16:21:47	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Declaracao_do_orientador_do_aluno.pdf	14/04/2018 11:18:21	FRANCELISE BRIDI CAVASSIN	Aceito
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Declaração de Manuseio Material	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito

Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Compromisso_de_utilizacao_de_dados.pdf	14/04/2018 11:12:42	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Responsabilidade.pdf	14/04/2018 11:10:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa.pdf	14/04/2018 11:09:57	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Qualificacao_dos_pesquisadores.pdf	14/04/2018 11:08:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Laboratorio.pdf	14/04/2018 11:07:35	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Farmacia.pdf	14/04/2018 11:06:31	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ausencia_de_Custos.pdf	14/04/2018 11:05:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CURITIBA, 04 de Julho de 2020

Assinado por:
Jeanine Marie Nardin
(Coordenador(a))

Endereço: Rua Dr. Ovande do Amaral 201
Bairro: Jardim das Américas **CEP:** 81.520-060
UF: PR **Município:** CURITIBA
Telefone: (41)3361-5271 **E-mail:** cep@erastogaertner.com.br

USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - HCFMUSP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: MARCELLO MIHAILENKO CHAVES MAGRI

Área Temática:

Versão: 1

CAAE: 87619218.5.2005.0068

Instituição Proponente: Instituto Central do HCFMUSP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.830.084

Apresentação do Projeto:

Pacientes com Infecções fúngicas invasivas são normalmente diagnosticados em hospitais públicos terciários e podem representar um desafio terapêutico para o sistema de saúde em países em desenvolvimento. No Brasil, poucas doenças fúngicas são notificadas ao Ministério da Saúde como coccidioidomicose, histoplasmose e paracoccidioidomicose, porém a carga de outras doenças fúngicas prevalentes no país é, ainda, desconhecida. As IFIs são difíceis de detectar e tratar e podem ser associadas à morbidade e mortalidade substanciais. O complexo lipídico de anfotericina B (ABELCET®) é fornecido pelo Ministério da Saúde brasileiro para tratamento de pacientes com infecções fúngicas invasivas, internados em hospitais da rede SUS. Apesar do uso frequente desse medicamento, dados disponíveis que exponham sua eficácia, tolerabilidade e segurança são escassos quando comparados a outras formulações disponíveis há mais tempo no mercado, como a anfotericina B-desoxicolato e a anfotericina B lipossomal. Através de um estudo de coorte multicêntrico, retro e prospectivo, que será conduzido em cinco hospitais terciários públicos brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR), será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade desse medicamento, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções.

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Objetivo da Pesquisa:

Avaliar e comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B (desoxicolato, lipossomal e complexo lipídico) em hospitais terciários brasileiros.

Avaliação dos Riscos e Benefícios:

Risco mínimo. Trata-se de estudo com prontuários de pacientes internados entre (2014 – 2018) e em (2019-2020). Pesquisador informa que serão adotados cuidados para minimizar riscos de identificação dos prontuários dos pacientes.

Comentários e Considerações sobre a Pesquisa:

Estudo bem desenhado acerca dos benefícios terapêuticos e da qualidade de medicamentos antifúngicos, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções.

Considerações sobre os Termos de apresentação obrigatória:

Dispensa de TCLE, pois trata-se de estudo com prontuários retrospectivo (2014-2018) e prospectivo (2019-2020).

Conclusões ou Pendências e Lista de Inadequações:

Aprovação

Considerações Finais a critério do CEP:

Em conformidade com a Resolução CNS nº 466/12 – cabe ao pesquisador: a) desenvolver o projeto conforme delineado; b) elaborar e apresentar relatórios parciais e final; c)apresentar dados solicitados pelo CEP, a qualquer momento; d) manter em arquivo sob sua guarda, por 5 anos da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP; e) encaminhar os resultados para publicação, com os devidos créditos aos pesquisadores associados e ao pessoal técnico participante do projeto; f) justificar perante ao CEP interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1435909.pdf	22/01/2020 16:40:07		Aceito
Outros	Termo_Usodados.pdf	22/01/2020 16:39:50	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito

Folha de Rosto	Folha_rosto.pdf	22/01/2020 10:39:01	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito
Outros	Termo_compromisso.pdf	22/01/2020 10:38:15	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito
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Outros	SEM_CUSTO.pdf	16/12/2019 15:11:28	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito
Outros	Documento_Depto.pdf	13/12/2019 16:05:56	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito
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Outros	Lista_participantes.docx	13/12/2019 15:58:53	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito
Outros	Parecer_anfotericinaB.pdf	26/11/2019 16:53:56	MARCELLO MIHAILENKO CHAVES MAGRI	Aceito
Outros	LISTA_DE_CENTROS_PARTICIPANTES_E_COPARTICIPANTES.docx	29/08/2019 17:45:29	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_centros.docx	29/08/2019 17:44:51	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_APRESENTACAO_E_JUSTIFICATIVA_PARA_EMENDA_AO_PROJETO.pdf	21/05/2019 09:40:48	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_ORIENTACAO.pdf	28/08/2018 13:58:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_CONFIDENCIALIDADE.pdf	28/08/2018 13:57:49	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_RESPONSABILIDADE.pdf	28/08/2018 13:57:06	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Outros	Instrumento_de_Pesquisa_2.pdf	29/05/2018 16:21:47	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_RESPOSTA_A_PENDENCIA.pdf	29/05/2018 16:20:01	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_do_orientador_do_aluno.pdf	14/04/2018 11:18:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Carta_de_encaminhamento.pdf	14/04/2018 11:17:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Confidencialidade.pdf	14/04/2018 11:16:35	FRANCELISE BRIDI CAVASSIN	Aceito
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Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Responsabilidade.pdf	14/04/2018 11:10:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa.pdf	14/04/2018 11:09:57	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Qualificacao_dos_pesquisadores.pdf	14/04/2018 11:08:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Laboratorio.pdf	14/04/2018 11:07:35	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Farmacia.pdf	14/04/2018 11:06:31	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ausencia_de_Custos.pdf	14/04/2018 11:05:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 10 de Fevereiro de 2020

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador(a))

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
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UFRGS - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE DA UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL ¿ HCPA

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: Flavio de Queiroz Telles Filho

Área Temática:

Versão: 1

CAAE: 87619218.5.3005.5327

Instituição Proponente: Hospitalde Clínicas de Porto Alegre

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.809.775

Apresentação do Projeto:

Em 16/01/2020 foi encaminhada ao CEP emenda que visa atualizar a equipe de pesquisa do projeto.

Objetivo da Pesquisa:

O objetivo da presente emenda é excluir uma pesquisadora da equipe.

Avaliação dos Riscos e Benefícios:

Não se aplica.

Comentários e Considerações sobre a Pesquisa:

Ec submetida em 16/01/2020.

Carta de justificativa adicionada em 05/12/2019:

Solicito Emenda para:

1) Exclusão de Assistente de Pesquisa

Endereço: Rua Ramiro Barcelos 2.350 sala 2229
Bairro: Santa Cecília **CEP:** 90.035-903
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3359-7640 **Fax:** (51)3359-7640 **E-mail:** cep@hcpa.edu.br

UFRGS - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE DA UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL ¿ HCPA

a) Justificativa para incluir esta emenda: a assistente de pesquisa já concluiu suas atividades perante o projeto.

b) Proposta da emenda: exclusão da assistente de pesquisa
1. Elaine Culig

c) Qual é a opinião e o posicionamento do pesquisador principal em relação ao desenvolvimento da pesquisa, frente ao documento apresentado: a acadêmica de medicina Elaine Culig participou em parte do projeto durante a realização de seu trabalho de conclusão do curso e agora, portanto, deixa de fazer parte da equipe de pesquisa.

Considerações sobre os Termos de apresentação obrigatória:
Foi incluída carta de justificativa.

Recomendações:
* Ressaltamos a equipe cadastrada na Plataforma Brasil deve estar de acordo com a equipe do presente centro cadastrada no sistema AGHUse Pesquisa e no Formulário de Delegação de Funções. Quando da submissão de uma próxima emenda devem ser revisadas estas questões.

Conclusões ou Pendências e Lista de Inadequações:
A emenda não apresenta pendências e está em condições de aprovação.

Considerações Finais a critério do CEP:
Ec submetida em 16/01/2020 aprovada, atualiza equipe de pesquisa.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	CARTA_PARA_EMENDA_exclusao_Elaine.docx	05/12/2019 14:24:34	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	LISTA_DE_CENTROS_PARTICIPANTES_E_COPARTICIPANTES.docx	29/08/2019 17:45:29	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_centros.docx	29/08/2019 17:44:51	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito

Endereço: Rua Ramiro Barcelos 2.350 sala 2229
Bairro: Santa Cecília **CEP:** 90.035-903
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3359-7640 **Fax:** (51)3359-7640 **E-mail:** cep@hcpa.edu.br

UFRGS - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE DA UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL ¿ HCPA

Continuação do Parecer: 3.809.775

Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_APRESENTACAO_E_JUSTIFICATIVA_PARA_EMENDA_AO_PROJETO.pdf	21/05/2019 09:40:48	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_ORIENTACAO.pdf	28/08/2018 13:58:26	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	TERMO_CONFIDENCIALIDADE.pdf	28/08/2018 13:57:49	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_RESPONSABILIDADE.pdf	28/08/2018 13:57:06	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa_2.pdf	29/05/2018 16:21:47	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_RESPOSTA_A_PENDENCIA.pdf	29/05/2018 16:20:01	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_do_orientador_do_aluno.pdf	14/04/2018 11:18:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Carta_de_encaminhamento.pdf	14/04/2018 11:17:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Confidencialidade.pdf	14/04/2018 11:16:35	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_de_tornar_publico_os_resultados.pdf	14/04/2018 11:15:48	FRANCELISE BRIDI CAVASSIN	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Compromisso_de_utilizacao_de_dados.pdf	14/04/2018 11:12:42	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Responsabilidade.pdf	14/04/2018 11:10:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa.pdf	14/04/2018 11:09:57	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Qualificacao_dos_pesquisadores.pdf	14/04/2018 11:08:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Laboratorio.pdf	14/04/2018	FRANCELISE BRIDI	Aceito

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Outros	Ausencia_de_Custos.pdf	14/04/2018 11:05:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 24 de Janeiro de 2020

Assinado por:
Marcia Mocellin Raymundo
(Coordenador(a))

Endereço: Rua Ramiro Barcelos 2.350 sala 2229
Bairro: Santa Cecília **CEP:** 90.035-903
UF: RS **Município:** PORTO ALEGRE
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HOSPITAL DE DOENÇAS TROPICAIS DR. ANUAR AUAD - HDT/HAA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: CASSIA SILVA MIRANDA GODOY

Área Temática:

Versão: 2

CAAE: 87619218.5.2004.0034

Instituição Proponente: Hospital Dr. Anuar Auad / HDT

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.941.040

Apresentação do Projeto:

O estudo já está em andamento e é multicêntrico, a proposição apresenta uma emenda com a inclusão do HDT. É uma pesquisa documental, em prontuários de pacientes internados que fizeram ou farão uso de Anfotericina B no período de 2014 a 2020. No HDT o estudo será apenas retrospectivo, não será analisado nenhum dado de pacientes em tratamento com Anfotericina no momento da coleta.

Objetivo da Pesquisa:

Objetivo Principal:

Avaliar e comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B (desoxicolato, lipossomal e complexo lipídico) em hospitais terciários brasileiros.

Objetivos Secundários

- Diferenciar, através de uma revisão de literatura, os aspectos farmacológicos das formulações de anfotericina B atualmente utilizadas para tratamento de infecções fúngicas invasivas;
- Coletar dados demográficos e epidemiológicos, fatores de risco e elementos farmacodinâmicos associados ao uso de anfotericina B obtidos em prontuários de pacientes diagnosticados com IFI e internados em hospitais da rede SUS;
- Analisar dados retrospectivos e prospectivos, obtidos em prontuários de pacientes internados no

CHC/UFPR, diagnosticados com IFI e tratados com diferentes formulações de anfotericina B.
- Comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B nos dados que serão pesquisados;
- Relatar os benefícios terapêuticos do complexo lipídico de anfotericina B (ABELCET®) quando comparado ao tratamento convencional e/ou lipossomal.

Avaliação dos Riscos e Benefícios:

Benefícios:

A pesquisa trará dados objetivos que possibilitarão a comaparação entre os fármacos, ampliando a segurança do tratamento.

Riscos:

O risco citado é o de exposição. Como estratégia de minimização, nos instrumentos de coleta de dados não se registra nenhum dado que possa levar à identificação dos participantes, os únicos dados demográficos registrados são sexo, idade, peso e altura.

Comentários e Considerações sobre a Pesquisa:

A pesquisa presenta grande relevância para subsidiar escolha terapêuticas mais seguras no uso da Anfotericina B.

Como a solicitação de coleta no HDT é exclusivamente de dados retrospectivos e muitos desses pacientes não mantem mais nenhum contato com essa instituição ou já faleceram, a dispensa do TCLE é justificável.

Considerações sobre os Termos de apresentação obrigatória:

Os pesquisadores apresentaram:

1. Autorização da Diretoria Geral e de Ensino e Pesquisa;
2. Autorização do DEAM;
3. TCUD's, um com assinatura do pesquisador principal e outro com a assinatura das pesquisadoras responsáveis pela coleta de dados no HDT;
4. Currículo Lattes.

Conclusões ou Pendências e Lista de Inadequações:

Emite-se parecer favorável à execução desta pesquisa conforme o protocolo apresentado, uma vez que está de acordo com a Resolução CNS 466/12.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1435908.pdf	19/02/2020 18:59:25		Aceito
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Outros	CV_cassiagodoy.pdf	19/02/2020 18:57:36	Renata de Bastos Ascenço Soares	Aceito
Folha de Rosto	doc15068820191127190531.pdf	27/11/2019 16:28:47	Renata de Bastos Ascenço Soares	Aceito
Outros	TCUD_HDT.pdf	27/11/2019 14:06:02	Renata de Bastos Ascenço Soares	Aceito
Outros	doc14997820191106221704FT.pdf	25/11/2019 19:06:48	Renata de Bastos Ascenço Soares	Aceito
Declaração de Instituição e Infraestrutura	doc14997720191106221642AIFT.pdf	25/11/2019 19:06:24	Renata de Bastos Ascenço Soares	Aceito
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Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	TERMO_COMPROMISSO.pdf	28/08/2018 13:58:05	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_CONFIDENCIALIDADE.pdf	28/08/2018 13:57:49	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito

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Outros	CARTA_RESPOSTA_A_PENDENCIA.pdf	29/05/2018 16:20:01	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_do_orientador_do_aluno.pdf	14/04/2018 11:18:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Carta_de_encaminhamento.pdf	14/04/2018 11:17:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Confidencialidade.pdf	14/04/2018 11:16:35	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_de_tornar_publico_os_resultados.pdf	14/04/2018 11:15:48	FRANCELISE BRIDI CAVASSIN	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Compromisso_de_utilizacao_de_dados.pdf	14/04/2018 11:12:42	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Qualificacao_dos_pesquisadores.pdf	14/04/2018 11:08:50	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

GOIANIA, 29 de Março de 2020

Assinado por:
Patricia Moreira de Araújo Lisbôa
(Coordenador(a))

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Bairro: Jardim Bela Vista **CEP:** 74.853-120
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HOSPITAL DE CRIANÇAS
CÉSAR PERNETTA E
HOSPITAL PEQUENO

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: Flavio de Queiroz Telles Filho

Área Temática:

Versão: 1

CAAE: 87619218.5.3003.0097

Instituição Proponente: Hospital Infantil Waldemar Monastier

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.020.515

Apresentação do Projeto:

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS BRASILEIROS

Pesquisador Responsável: Flavio de Queiroz Telles Filho

Objetivo da Pesquisa:

EMENDA com objetivo de:

1) Inclusão de novo Centro Participante.

a) Justificativa para incluir esta emenda: aceite de novo pesquisador após convite de participação nesse estudo.

b) Proposta da emenda: inclusão do centro participante

1. Hospital Universitário do Oeste do Paraná (HUOP/PR)

c) Qual é a opinião e o posicionamento do pesquisador principal em relação ao desenvolvimento da pesquisa, frente ao documento apresentado: como consta na primeira versão do projeto, os centros foram definidos após algumas reuniões que aconteceram em Brasília, na qual os pesquisadores foram

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UF: PR **Município:** CURITIBA
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convidados e puderam demonstrar interesse em participar do estudo multicêntrico. Nesse momento, mais um deles (Dra. Carla Sakuma de Oliveira) aceitou participar.

Avaliação dos Riscos e Benefícios:

Os riscos e benefícios permanecem os mesmos conforme protocolo aprovado;

Comentários e Considerações sobre a Pesquisa:

Emenda esclarecida em termo em anexo;

Considerações sobre os Termos de apresentação obrigatória:

Os termos são:

- CARTA_PARA_EMENDA_inclusao_HUOP.pdf / Word

Conclusões ou Pendências e Lista de Inadequações:

Emenda Aprovada;

Considerações Finais a critério do CEP:

Lembramos que conforme as normas da CONEP/MS o pesquisador deverá enviar ao CEP relatórios semestrais sobre o andamento do estudo, bem como a qualquer tempo e a critério do pesquisador em caso de relevância. Salientamos ainda a necessidade do envio do relatório final do estudo.Retirar o (TCLE)Termo de Consentimento e TALE- Termo de Assentimento (quando for o caso) com rubrica e carimbo para aplicá-los. Uma deve ficar com o responsável legal e/ou participante da pesquisa, e outra com o pesquisador responsável. As vias devem ser assinadas por todos.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	CARTA_PARA_EMENDA_alteracao_UNIFESP.docx	24/04/2020 17:34:05	FRANCELISE BRIDI CAVASSIN	Aceito
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HOSPITAL DE CRIANÇAS
CÉSAR PERNETTA E
HOSPITAL PEQUENO

Continuação do Parecer: 4.020.515

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Outros	Qualificacao_dos_pesquisadores.pdf	14/04/2018 11:08:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Laboratorio.pdf	14/04/2018	FRANCELISE BRIDI	Aceito

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UF: PR **Município:** CURITIBA
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HOSPITAL DE CRIANÇAS
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HOSPITAL PEQUENO

Continuação do Parecer: 4.020.515

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Outros	Ausencia_de_Custos.pdf	14/04/2018 11:05:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CURITIBA, 11 de Maio de 2020

Assinado por:
NILTON KIESEL FILHO
(Coordenador(a))

Endereço: Rua Desembargador Motta, nº 1070
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HOSPITAL SÃO RAFAEL

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: Flavio de Queiroz Telles Filho

Área Temática:

Versão: 1

CAAE: 87619218.5.3006.0048

Instituição Proponente: HOSPITAL SAO RAFAEL S.A

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.036.845

Apresentação do Projeto:

Infecções fúngicas invasivas (IFIs) são de importância e interesse global. Pacientes com IFI grave são normalmente diagnosticados em hospitais públicos terciários e podem representar um desafio terapêutico para o sistema de saúde em países em desenvolvimento. Estima-se que, no mundo, mais de um bilhão de pessoas sofrem de uma infecção fúngica e que mais de 1,5 milhão de pessoas morrem a cada ano de uma infecção fúngica. No Brasil, poucas doenças fúngicas são notificadas ao Ministério da Saúde como coccidioidomicose, histoplasmose e paracoccidioidomicose, porém a carga de outras doenças fúngicas prevalentes no país é, ainda, desconhecida. As IFIs são difíceis de detectar e tratar e podem ser associadas à morbidade e mortalidade substanciais. O complexo lipídico de anfotericina B (ABELCET®) é fornecido pelo Ministério da Saúde brasileiro para o tratamento de pacientes com infecções fúngicas invasivas, internados em hospitais da rede SUS. Apesar do uso frequente desse medicamento, dados disponíveis que exponham sua eficácia, tolerabilidade e segurança são escassos quando comparados a outras formulações disponíveis há mais tempo no mercado, como a anfotericina B-desoxicolato e a anfotericina B lipossomal. Através de

um estudo de coorte multicêntrico, retro e prospectivo, que será conduzido em cinco hospitais terciários públicos brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR), será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade desse medicamento, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Objetivo da Pesquisa:

Avaliar e comparar a eficácia, tolerabilidade e
segurança das diferentes formulações de anfotericina B (desoxicolato, lipossomal e complexo lipídico) em hospitais terciários brasileiros.

Objetivo(s) Secundário(s)

- Diferenciar, através de uma revisão de literatura, os aspectos farmacológicos das formulações de anfotericina B atualmente utilizadas para tratamento de infecções fúngicas invasivas;
- Coletar dados demográficos e epidemiológicos, fatores de risco e elementos farmacodinâmicos associados ao uso de anfotericina B obtidos em prontuários de pacientes diagnosticados com IFI e internados em hospitais da rede SUS;
- Analisar dados retrospectivos e prospectivos, obtidos em prontuários de pacientes internados no CHC/UFPR, diagnosticados com IFI e tratados com diferentes formulações de anfotericina B.
- Comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B nos dados que serão pesquisados;
- Relatar os benefícios terapêuticos do complexo lipídico de anfotericina B (ABELCET®) quando comparado ao tratamento convencional e/ou lipossomal.

Avaliação dos Riscos e Benefícios:

Benefícios

Através desse estudo, será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade de medicamentos antifúngicos, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais

infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Riscos

Quebra de anonimato: os riscos serão minimizados através da não utilização de nomes ou siglas que possam, eventualmente, identificar os prontuários de pacientes que serão avaliados na pesquisa. O instrumento de coleta de dados utilizará variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da infecção fúngica invasiva, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos e serão coletados exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo.

Comentários e Considerações sobre a Pesquisa:

As descrições dos aspectos farmacológicos relacionados com seus efeitos de tolerabilidade e toxicidade avaliados na prática trarão um impacto científico significativo. No campo da terapêutica das infecções fúngicas invasivas esta pesquisa se torna relevante, pois é necessária a busca por evidências que apontem a eficácia e a segurança dos medicamentos antifúngicos distribuídos amplamente nos hospitais públicos terciários brasileiros e que são fornecidos gratuitamente pelo Sistema Único de Saúde.

Considerações sobre os Termos de apresentação obrigatória:

Todos documentos apresentados.

Recomendações:

Todas recomendações estão inseridas

Conclusões ou Pendências e Lista de Inadequações:

Aprovado para seguimento.

Considerações Finais a critério do CEP:

Colegiado acata parecer do relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	CARTA_PARA_EMENDA_inclusao_HU	13/03/2020	FRANCELISE BRIDI	Aceito

Continuação do Parecer: 4.036.845

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Outros	LISTA_DE_CENTROS_PARTICIPANTES_E_COPARTICIPANTES.docx	29/08/2019 17:45:29	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_centros.docx	29/08/2019 17:44:51	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_APRESENTACAO_E_JUSTIFICATIVA_PARA_EMENDA_AO_PROJETO.pdf	21/05/2019 09:40:48	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_ORIENTACAO.pdf	28/08/2018 13:58:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_COMPROMISSO.pdf	28/08/2018 13:58:05	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_CONFIDENCIALIDADE.pdf	28/08/2018 13:57:49	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_RESPONSABILIDADE.pdf	28/08/2018 13:57:06	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa_2.pdf	29/05/2018 16:21:47	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_RESPOSTA_A_PENDENCIA.pdf	29/05/2018 16:20:01	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_do_orientador_do_aluno.pdf	14/04/2018 11:18:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Carta_de_encaminhamento.pdf	14/04/2018 11:17:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Confidencialidade.pdf	14/04/2018 11:16:35	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_de_tornar_publico_os_resultados.pdf	14/04/2018 11:15:48	FRANCELISE BRIDI CAVASSIN	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Compromisso_de_utilizacao_de_dados.pdf	14/04/2018 11:12:42	FRANCELISE BRIDI CAVASSIN	Aceito

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UF: BA **Município:** SALVADOR
Telefone: (71)3281-6484 **Fax:** (71)3281-6855 **E-mail:** cep@hsr.com.br

Outros	Termo_de_Responsabilidade.pdf	14/04/2018 11:10:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa.pdf	14/04/2018 11:09:57	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Concordancia_Farmacia.pdf	14/04/2018 11:06:31	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ausencia_de_Custos.pdf	14/04/2018 11:05:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SALVADOR, 19 de Maio de 2020

Assinado por:
Lucas de Oliveira Vieira
(Coordenador(a))

INSTITUTO DE INFECTOLOGIA
EMÍLIO RIBAS - IIER

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: JOSE ERNESTO VIDAL BERMUDEZ

Área Temática:

Versão: 1

CAAE: 87619218.5.2001.0061

Instituição Proponente: Instituto de Infectologia Emílio Ribas

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.687.034

Apresentação do Projeto:

Trata-se de uma pesquisa aplicada, de natureza observacional (estudo de coorte) e abordagem mista, do tipo documental. O estudo de coorte multicêntrico, retro e prospectivo, será conduzido em 5 hospitais terciários públicos brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR). Além do centro coordenador já determinado para o estudo (Complexo Hospital de Clínicas da Universidade Federal do Paraná), os demais hospitais que participarão desta pesquisa foram definidos após reuniões realizadas no Ministério da Saúde, em Brasília. No momento os centros que já concordaram a participar do estudo são: Hospital Pequeno Príncipe (PR); Instituto de Infectologia Emilio Ribas (SP); Hospital de Clínicas de Porto Alegre (RS); Grupo de Apoio ao Adolescente e a Criança com Câncer (SP); Hospital Erasto Gaertner (PR); Hospital São Rafael de Salvador (BA). Técnicas de Coleta de Dados, de natureza observacional e do tipo documental, variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da IFI, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos serão coletados exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo. Para isso duas fichas serão criteriosamente elaboradas: Ficha 1 - Ficha de dados retrospectivos de 2014 a 2018 (em formato de formulário eletrônico para estudo multicêntrico); Ficha 2 - Ficha de dados prospectivos

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(adaptado de FALCI, 2015). Basicamente, a diferença entre as fichas é que os dados prospectivos serão coletados em um formulário de registro mais detalhado. Em hipótese alguma o investigador poderá interferir nos padrões do hospital em relação ao tratamento dos pacientes com infecções fúngicas invasivas. Para padronização das definições dos dados, em cada ficha constará um dicionário de termos, expondo exatamente como a variável deverá ser coletada. Todas as informações para preenchimento dos dados serão obtidas de prontuários médicos. No centro coordenador (HC/UFPR), serão avaliados todos os elementos em relação à consistência das fichas. Dados inconsistentes serão reenviados aos centros de origem para esclarecimento ou correção.
Através do estudo será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade desse medicamento, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.
Tamanho da Amostra no Brasil: 300

Critério de Inclusão:
Serão incluídos na coorte restrospectiva, prontuários de pacientes que preencham os seguintes critérios:- que tenham sido internados nos cinco hospitais públicos terciários pré-determinados, nos últimos cinco anos (2014 a 2018); - que tenham sido diagnosticados com algum tipo de infecção fúngica invasiva no mesmo período; - que tenham sido tratados com pelo menos uma das seguintes formulações de anfotericina B: desoxicolato, lipossomal e complexo lipídico.Serão incluídos na coorte prospectiva, prontuários de pacientes que preencham os seguintes critérios:- estarem internados no Complexo Hospital de Clínicas da Universidade Federal do Paraná no período do próximo ano do estudo (2019 – 2020);- serem diagnosticados com algum tipo de infecção fúngica invasiva no mesmo período;- sendo tratados com pelo menos uma das seguintes formulações de anfotericina B: desoxicolato, lipossomal e complexo lipídico.

Critério de Exclusão:
Serão excluídos todos os prontuários que não atendam aos critérios de inclusão citados.

Haverá uso de fontes secundárias de dados. De natureza observacional e do tipo documental, variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da

IFI, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos serão coletados exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo.

Propõe dispensa do TCLE. Justificativa: Ambas as fases do estudo (retro e prospectivo) não envolverá qualquer contato com o paciente, somente coleta de dados a partir de seus prontuários. O estudo de coorte prospectivo será realizado no Centro Coordenador desse estudo, ou seja, o Complexo Hospital de Clínicas da Universidade Federal do Paraná. Em hipótese alguma o investigador irá interferir nos padrões do hospital em relação ao tratamento farmacológico dos pacientes diagnosticados com infecções fúngicas invasivas.

Outras informações, justificativas ou considerações a critério do pesquisador:
Além do centro coordenador já determinado para o estudo (Complexo Hospital de Clínicas da Universidade Federal do Paraná), os demais hospitais que participarão desta pesquisa serão definidos após uma reunião a ser realizada no Ministério da Saúde, em Brasília, no dia 23 de maio, e que contará com a participação de representantes do Grupo Técnico de Micoses Sistêmicas da Secretaria de Vigilância em Saúde (SVS) do Ministério da Saúde do Brasil. Após a definição, cada centro participante contará com um investigador que será responsável pela coleta e envio dos dados. Assim que esses locais forem definidos, uma emenda será criada e complementada junto ao CEP via Plataforma Brasil. Observação Participante: Será apenas solicitada a dispensa de assinatura do TCLE para os pacientes não acessíveis (casos de óbito, perda de seguimento, abandono de tratamento, mudança de residência para outro estado).

Objetivo da Pesquisa:
Objetivo Primário:
Avaliar e comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B (desoxicolato, lipossomal e complexo lipídico) em hospitais terciários brasileiros.

Objetivo Secundário:
Diferenciar, através de uma revisão de literatura, os aspectos farmacológicos das formulações de anfotericina B atualmente utilizadas para tratamento de infecções fúngicas invasivas; Coletar dados demográficos e epidemiológicos, fatores de risco e elementos farmacodinâmicos associados ao uso de anfotericina B obtidos em prontuários de pacientes diagnosticados com IFI e internados

em hospitais da rede SUS; Analisar dados retrospectivos e prospectivos, obtidos em prontuários de pacientes internados no CHC/UFPR, diagnosticados com IFI e tratados com diferentes formulações de anfotericina B.Comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B nos dados que serão pesquisados;Relatar os benefícios terapêuticos do complexo lipídico de anfotericina B (ABELCET®) quando comparado ao tratamento convencional e/ou lipossomal.

Avaliação dos Riscos e Benefícios:

Riscos:

Quebra de anonimato: os riscos serão minimizados através da não utilização de nomes ou siglas que possam, eventualmente, identificar os prontuários de pacientes que serão avaliados na pesquisa. O instrumento de coleta de dados utilizará variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da infecção fúngica invasiva, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos e serão coletados exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo.

Benefícios:

Através desse estudo, será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade de medicamentos antifúngicos, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Comentários e Considerações sobre a Pesquisa:

Estudo de relevância que possibilitara a avaliação da efetividade, tolerabilidade e segurança das diferentes formulações de anfotericina B.

Considerações sobre os Termos de apresentação obrigatória:

-Termo de Consentimento Livre e Esclarecido Para Utilização de Informações de Prontuário adequado.

-Termo de Confidencialidade adequado.

Recomendações:

Verificar conclusões

Conclusões ou Pendências e Lista de Inadequações:

CEP toma ciência e aprova o projeto de pesquisa acima citado.

Considerações Finais a critério do CEP:

O pesquisador deverá entregar uma cópia do Parecer de Aprovação do CEP à Seção de Pesquisa e Trabalhos Científicos da Divisão Científica e aguardar o documento denominado "Autorização Para o Início do Estudo". O pesquisador principal deverá enviar a este CEP os relatórios parciais e do final do estudo, conforme prevê a Resolução CNS nº 466/2012.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1415507.pdf	29/10/2019 19:37:26		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_IIER_AnfoB.docx	29/10/2019 19:24:21	Rosa Maria Nascimento Marcusso	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_IIER_AnfoB.pdf	29/10/2019 19:24:09	Rosa Maria Nascimento Marcusso	Aceito
Outros	Confidencialidade_IIER.pdf	26/09/2019 19:47:29	Rosa Maria Nascimento Marcusso	Aceito
Folha de Rosto	FolhaRosto_AnfoB.pdf	26/09/2019 19:46:05	Rosa Maria Nascimento Marcusso	Aceito
Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_APRESENTACAO_E_JUSTIFICATIVA_PARA_EMENDA_AO_PROJETO.pdf	21/05/2019 09:40:48	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_ORIENTACAO.pdf	28/08/2018 13:58:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_COMPROMISSO.pdf	28/08/2018 13:58:05	FRANCELISE BRIDI CAVASSIN	Aceito

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Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Declaracao_de_tornar_publico_os_resultados.pdf	14/04/2018 11:15:48	FRANCELISE BRIDI CAVASSIN	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Compromisso_de_utilizacao_de_dados.pdf	14/04/2018 11:12:42	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Instrumento_de_Pesquisa.pdf	14/04/2018 11:09:57	FRANCELISE BRIDI CAVASSIN	Aceito
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Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 06 de Novembro de 2019

Assinado por:
Vilma Borba Leandro Ferreira Jardim
(Coordenador(a))

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UNIVERSIDADE FEDERAL DE SÃO PAULO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO MULTICÊNTRICO PARA AVALIAÇÃO DA EFETIVIDADE, TOLERABILIDADE E SEGURANÇA DAS DIFERENTES FORMULAÇÕES DE ANFOTERICINA B EM HOSPITAIS PÚBLICO-PRIVADOS TERCIÁRIOS

Pesquisador: Fabianne Altruda de Moraes Costa Carlesse

Área Temática:

Versão: 2

CAAE: 87619218.5.2007.5505

Instituição Proponente: UNIVERSIDADE FEDERAL DE SAO PAULO

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.261.259

Apresentação do Projeto:

-Projeto CEP/UNIFESP n:0694/2020 Centro Participante (Parecer final)

-Trata-se de Projeto submetido em nome de Profa. Dra. Fabianne Altruda de Moraes Costa Carlesse (não envolve a obtenção de titulação acadêmica);

-Projeto vinculado ao Departamento de Pediatria, Campus São Paulo, Escola Paulista de Medicina, UNIFESP.

- Estudo Multicêntrico no Brasil: participarão 7 centros brasileiros.

-Centros Coparticipantes: participarão 4 centros Coparticipantes;

- Centro Coordenador: Complexo Hospital de Clínicas da Universidade Federal do Paraná – CHC/UFPR.

-As informações elencadas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1554336.pdf, gerado em 17/6/2020)

APRESENTAÇÃO: Infecções fúngicas invasivas (IFIs) são de importância e interesse global. Pacientes com IFI grave são normalmente diagnosticados em hospitais públicos terciários e podem representar um desafio terapêutico para o sistema de saúde em países em desenvolvimento.

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Estima-se que, no mundo, mais de um bilhão de pessoas sofrem de uma infecção fúngica e que mais de 1,5 milhão de pessoas morrem a cada ano de uma infecção fúngica. No Brasil, poucas doenças fúngicas são notificadas ao Ministério da Saúde como coccidioidomicose, histoplasmose e paracoccidioidomicose, porém a carga de outras doenças fúngicas prevalentes no país é, ainda, desconhecida. As IFIs são difíceis de detectar e tratar e podem ser associadas à morbidade e mortalidade substanciais. O complexo lipídico de anfotericina B (ABELCET®) é fornecido pelo Ministério da Saúde brasileiro para o tratamento de pacientes com infecções fúngicas invasivas, internados em hospitais da rede SUS. Apesar do uso frequente desse medicamento, dados disponíveis que exponham sua eficácia, tolerabilidade e segurança são escassos quando comparados a outras formulações disponíveis há mais tempo no mercado, como a anfotericina B-desoxicolato e a anfotericina B lipossomal. Através de um estudo de coorte multicêntrico, retro e prospectivo, que será conduzido em cinco hospitais terciários públicos brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR), será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade desse medicamento, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.
-HIPÓTESE: Espera-se que o complexo lipídico de anfotericina B (ABELCET®), fornecido pelo Ministério da Saúde brasileiro para o tratamento de pacientes com infecções fúngicas invasivas, apresente dados positivos (benéficos) de eficácia, tolerabilidade e segurança quando comparados a outras formulações de anfotericina B disponíveis a mais tempo no mercado.

Objetivo da Pesquisa:
-OBJETIVO PRIMÁRIO: Avaliar e comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B (desoxicolato, lipossomal e complexo lipídico) em hospitais terciários brasileiros.
-OBJETIVO SECUNDÁRIO: Diferenciar, através de uma revisão de literatura, os aspectos farmacológicos das formulações de anfotericina B atualmente utilizadas para tratamento de infecções fúngicas invasivas;Coletar dados demográficos e epidemiológicos, fatores de risco e elementos farmacodinâmicos associados ao uso de anfotericina B obtidos em prontuários de pacientes diagnosticados com IFI e internados em hospitais da rede SUS;Analisar dados retrospectivos e prospectivos, obtidos em prontuários de pacientes internados no CHC/UFPR,

diagnosticados com IFI e tratados com diferentes formulações de anfotericina B.Comparar a eficácia, tolerabilidade e segurança das diferentes formulações de anfotericina B nos dados que serão pesquisados;Relatar os benefícios terapêuticos do complexo lipídico de anfotericina B (ABELCET®) quando comparado ao tratamento convencional e/ou lipossomal.

Avaliação dos Riscos e Benefícios:

Em relação aos riscos e benefícios, o pesquisador declara:

-RISCOS: Quebra de anonimato: os riscos serão minimizados através da não utilização de nomes ou siglas que possam, eventualmente, identificar os prontuários de pacientes que serão avaliados na pesquisa. O instrumento de coleta de dados utilizará variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da infecção fúngica invasiva, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos e serão coletados exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo.

-BENEFÍCIOS: Através desse estudo, será cabível a disponibilização, a nível nacional e internacional, de novas informações acerca dos benefícios terapêuticos e da qualidade de medicamentos antifúngicos, possibilitando maior segurança durante o tratamento de pacientes hospitalizados com tais infecções. Além do mais, o levantamento da eficácia e da toxicidade dentre esses compostos permitirá avaliar de forma importante, consequências significativas do ponto de vista de desfechos clínicos e custos hospitalares.

Comentários e Considerações sobre a Pesquisa:

TIPO DE ESTUDO: Trata-se uma pesquisa aplicada, de natureza observacional (estudo de coorte) e abordagem mista, do tipo documental. O estudo de coorte multicêntrico, retro e prospectivo, será conduzido em hospitais público-privados terciários brasileiros tendo como centro coordenador o Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR).

LOCAL: Grupo de Apoio ao Adolescente e a Criança com Câncer – GRAACC.

PARTICIPANTES: Serão incluído no GRAACC 100 pacientes

-Critério de Inclusão: Serão incluídos na coorte restrospectiva, prontuários de pacientes que preencham os seguintes critérios:- que tenham sido internados nos cinco hospitais públicos terciários pré-determinados, nos últimos cinco anos (2014 – 2018);- que tenham sido diagnosticados com algum tipo de infecção fúngica invasiva no mesmo período;- que tenham sido

tratados com pelo menos uma das seguintes formulações de anfotericina B: desoxicolato, lipossomal e complexo lipídico. Serão incluídos na coorte prospectiva, prontuários de pacientes que preencham os seguintes critérios:- estarem internados no Complexo Hospital de Clínicas da Universidade Federal do Paraná no período do próximo ano do estudo (2019 – 2020);- serem diagnosticados com algum tipo de infecção fúngica invasiva no mesmo período;- sendo tratados com pelo menos uma das seguintes formulações de anfotericina B: desoxicolato, lipossomal e complexo lipídico.
-Critério de Exclusão: Serão excluídos todos os prontuários que não atendam aos critérios de inclusão citados.

PROCEDIMENTOS: Além do centro coordenador já determinado para o estudo (Complexo Hospital de Clínicas da Universidade Federal do Paraná), os demais hospitais que participarão desta pesquisa foram definidos após reuniões realizadas no Ministério da Saúde, em Brasília. No momento os centros que já concordaram a participar do estudo são: Hospital Pequeno Príncipe (PR); Instituto de Infectologia Emilio Ribas (SP); Hospital de Clínicas de Porto Alegre (RS); Grupo de Apoio ao Adolescente e a Criança com Câncer (SP); Hospital Erasto Gaertner (PR); Hospital São Rafael de Salvador (BA); Hospital de Clínicas de São Paulo (HC/SP).
-Técnicas de Coleta de Dados: De natureza observacional e do tipo documental, variáveis como fatores de risco, manifestações clínicas, exames laboratoriais, diagnósticos além da IFI, resposta à terapia dos pacientes que receberam diferentes formulações de anfotericina B bem como dados sobre toxicidade e tolerabilidade a esses medicamentos serão coletados exclusivamente de prontuários de pacientes internados nos hospitais públicos terciários participantes do estudo.
-Para isso duas fichas serão criteriosamente elaboradas:- Ficha 1 - Ficha de dados retrospectivos (em formato de formulário eletrônico para estudo multicêntrico);- Ficha 2 - Ficha de dados prospectivos (adaptado de FALCI, 2015).Basicamente, a diferença entre as fichas é que os dados prospectivos serão coletados em um formulário de registro mais detalhado. Em hipótese alguma o investigador poderá interferir nos padrões do hospital em relação ao tratamento dos pacientes com infecções fúngicas invasivas. O desenho do modelo primário dessas fichas se encontra em anexo no final desse projeto. Para padronização das definições dos dados, em cada ficha constará um dicionário de termos, expondo exatamente como a variável deverá ser coletada. Todas as informações para preenchimento dos dados serão obtidas de prontuários médicos. No centro coordenador (HC/UFPR), serão avaliados todos os elementos em relação à consistência das fichas. Dados inconsistentes serão reenviados aos centros de origem para esclarecimento ou correção.

(mais informações, ver projeto detalhado).

Considerações sobre os Termos de apresentação obrigatória:

1- Foram apresentados os principais documentos: folha de rosto; projeto completo; cópia do cadastro CEP/UNIFESP, orçamento financeiro e cronograma apresentados.

2- Propõe dispensa do TCLE. Justificativa: Ambas as fases do estudo (retro e prospectivo) não envolverá qualquer contato com o paciente, somente coleta de dados a partir de seus prontuários. O estudo de coorte prospectivo será realizado no Centro Coordenador desse estudo, ou seja, o Complexo Hospital de Clínicas da Universidade Federal do Paraná. Em hipótese alguma o investigador irá interferir nos padrões do hospital em relação ao tratamento farmacológico dos pacientes diagnosticados com infecções fúngicas invasivas.

3- outros documentos importantes anexados na Plataforma Brasil:

a)- Aprovação do Comitê Científico do GRAACC (Aprovacao_IOP.pdf , postado em 15/6/2020)

b)- Carta de encaminhamento, assinada pela pesquisadora responsável pelo projeto, Dra. Fabianne Altruda de Moraes Costa Carlesse. (encaminhamento_cienciapdf.pdf, postado em 15/6/2020).

Recomendações:

Sem recomendações.

Conclusões ou Pendências e Lista de Inadequações:

Respostas ao parecer nº 4161806 de 18 de Julho de 2020.

PENDÊNCIA 1- No formulário de informações básicas da Plataforma Brasil, campo critérios de inclusão, foi informado que para a etapa prospectiva, serão acessados prontuários de pacientes internados no Complexo Hospital de Clínicas da Universidade Federal do Paraná (centro coordenador). Solicitamos esclarecer: a etapa prospectiva só será realizada no Centro Coordenador?

RESPOSTA PESQUISADOR: A etapa prospectiva será executada apenas no Centro Coordenador (Complexo Hospital de Clínicas da Universidade Federal do Paraná) ficando sob a responsabilidade dos pesquisadores dos Centros Participantes, a execução da etapa retrospectiva. Nenhum documento precisou ser alterado em resposta à essa pendência.

PENDÊNCIA ATENDIDA

PENDÊNCIA 2- Solicitamos informar quantos pacientes do GRAACC/UNIFESP estão previstos para serem incluídos?

RESPOSTA PESQUISADOR: O GRAACC pretende incluir dados de 100 pacientes. Nenhum documento precisou ser alterado em resposta à essa pendência.
PENDÊNCIA ATENDIDA

PENDÊNCIA 3- Atenção: no documento Carta de encaminhamento, assinada pela pesquisadora responsável pelo projeto, Dra. Fabianne Altruda de Moraes Costa Carlesse (encaminhamento_cienciapdf.pdf, postado em 15/6/2020) foi citada a Resolução Normativa 196/96. Lembramos que essa resolução já foi revogada, estando em vigor a Resolução Normativa 466/12 do CNS/MS, que aprova as normas e diretrizes regulamentadoras de pesquisa envolvendo seres humanos.
RESPOSTA PESQUISADOR: Essa informação foi atualizada e compõe também o documento intitulado "Declaração de Compromisso de Investigador", que se segue em anexo à essa carta. Um novo documento foi elaborado e, portanto, não se aplicam as orientações de destaque das alterações em documento anterior.
PENDÊNCIA ATENDIDA

PENDÊNCIA 4- Em relação ao pedido de dispensa de TCLE: Na presente pesquisa, a dispensa foi solicitada, com a justificativa de se tratar de análise retrospectiva de prontuários. O CEP/UNIFESP não aceita essa justificativa, uma vez, por orientação da CONEP, é considerado que a análise de prontuários não desobriga o pedido de TCLE, o qual deve ser aplicado no sentido de pedir autorização para o seu acesso, já que o prontuário é de propriedade do paciente e não do médico ou do pesquisador (conforme disposto pelo CFM). Dessa forma, deve ser tentado o contato com os pacientes para solicitar autorização para o acesso ao prontuário, por meio do Termo de Consentimento Livre e Esclarecido (TCLE). Solicitamos anexar o modelo de TCLE, ou solicitar dispensa com uma justificativa mais viável.
-A dispensa poderá ser concedida, se o pesquisador receber o banco de dados já anonimizado, de forma que não seja possível a identificação individual dos participantes.
Ou seja, se a anonimização for realizada por uma terceira pessoa que não esteja envolvida na pesquisa. E neste caso, deverá estar descrito no projeto quem irá realizar a anonimização e quais serão as formas de anonimização dos dados. Será necessário ainda, que seja anexada na Plataforma, uma declaração, assinada pelo profissional que realizará a anonimização, de que os dados serão fornecidos na forma anonimizada e de que há o compromisso de garantia de sigilo em relação a esses dados. Se a anonimização não for possível, será necessária a inclusão do

modelo de TCLE a ser aplicado aos participantes, solicitando autorização para o acesso ao prontuário.
-Para evitar novas pendências, se for o caso de elaborar o TCLE, verifique o modelo de TCLE na página da CEP/UNIFESP, link: UNIFESP - Pesquisa - Comitê de Ética em Pesquisa – Projeto envolvendo seres humanos -Plataforma Brasil: Modelo de TCLE em: https://cep.unifesp.br/links-uteis#modelos (A tomada de consentimento para a participação em pesquisa é procedimento obrigatório previsto na Resolução CNS n° 466 de 2012 e em diversos documentos internacionais de referência em ética em pesquisa. É importante esclarecer que uma dispensa de TCLE está condicionada a uma avaliação criteriosa dos argumentos elencados, de acordo com a Resolução 466/2012 -IV.8: Nos casos em que seja inviável a obtenção do Termo de Consentimento Livre e Esclarecido ou que esta obtenção signifique riscos substanciais à privacidade e confidencialidade dos dados do participante ou aos vínculos de confiança entre pesquisador e pesquisado, a dispensa do TCLE deve ser justificadamente solicitada pelo pesquisador responsável ao Sistema CEP/CONEP).
RESPOSTA PESQUISADOR: O GRAACC mantém um banco de dados de pacientes com diagnósticos de infecção fúngica para controle interno do número de incidência e para direcionamento e manejo do tratamento. Esse banco de dados será adequado a fim de anonimizar os dados sensíveis e identificáveis desses pacientes para que os dados possam ser utilizados para a referida pesquisa. Segue em anexo, o documento intitulado “Declaração de Adequação do Banco de Dados”, com maiores detalhes sobre ação. Um novo documento foi elaborado e, portanto, não se aplicam as orientações de destaque das alterações em documento anterior.
PENDÊNCIA ATENDIDA

PENDÊNCIA 5- Deve ser enviada declaração, assinada pelo pesquisador principal, de garantia de sigilo e anonimização dos dados e de responsabilização por qualquer problema em relação a quebra de sigilo dos participantes. Neste documento deve constar que o pesquisador está ciente que deverá orientar os demais pesquisadores envolvidos no projeto sobre o sigilo e a anonimização dos dados.
RESPOSTA PESQUISADOR: O documento intitulado “Declaração de Compromisso de Investigador” foi elaborado para contemplar essa exigência. O documento segue em anexo à essa carta. Um novo documento foi elaborado e, portanto, não se aplicam as orientações de destaque das alterações em documento anterior.
PENDÊNCIA ATENDIDA

Considerações Finais a critério do CEP:

1 - O CEP informa que a partir desta data de aprovação toda proposta de modificação ao projeto original deverá ser encaminhada por meio de emenda pela Plataforma Brasil.

2 - O CEP informa que a partir desta data de aprovação, é necessário o envio de relatórios parciais (semestralmente), e o relatório final, quando do término do estudo, por meio de notificação pela Plataforma Brasil.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1554336.pdf	18/08/2020 14:17:54		Aceito
Outros	ANFOTERICINA_CARTARESPOSTA_GRAACC_DraFabianne.pdf	18/08/2020 14:16:34	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Outros	ANFOTERICINA_CARTARESPOSTA_GRAACC_DraFabianne_Retificada.docx	18/08/2020 14:16:21	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Outros	ANFOTERICINA_Declaracao_Adequacao_Banco_Dados_GRAACC_DraFabianne.docx	30/07/2020 16:55:35	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Declaração de concordância	ANFOTERICINA_Declaracao_Adequacao_Banco_Dados_GRAACC_DraFabianne.pdf	30/07/2020 16:53:53	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Declaração de Pesquisadores	ANFOTERICINA_Declaracao_Compromisso_Investigador_GRAACC_DraFabianne.pdf	30/07/2020 16:53:20	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Declaração do Patrocinador	ANFOTERICINA_Declaracao_Compromisso_Investigador_GRAACC_DraFabianne.docx	30/07/2020 16:53:05	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Outros	ANFOTERICINA_Carta_Encaminhamento_GRAACC_DraFabianne.pdf	30/07/2020 16:52:51	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Outros	ANFOTERICINA_Carta_Encaminhamento_GRAACC_DraFabianne.docx	30/07/2020 16:52:34	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Solicitação registrada pelo CEP	CEPUNIFESP.pdf	17/06/2020 16:09:42	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Folha de Rosto	folhaderosto.pdf	17/06/2020 16:09:13	Fabianne Altruda de Moraes Costa Carlesse	Aceito

Declaração de Instituição e Infraestrutura	Aprovacao_IOP.pdf	15/06/2020 12:58:51	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Outros	encaminhamento_cienciapdf.pdf	15/06/2020 12:32:21	Fabianne Altruda de Moraes Costa Carlesse	Aceito
Outros	CARTA_PARA_EMENDA_alteracao_UNIFESP.docx	24/04/2020 17:34:05	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_HUOP.pdf	13/03/2020 10:00:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_exclusao_Elaine.docx	05/12/2019 14:24:34	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	LISTA_DE_CENTROS_PARTICIPANTES_E_COPARTICIPANTES.docx	29/08/2019 17:45:29	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_EMENDA_inclusao_centros.docx	29/08/2019 17:44:51	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ficha_Clinica_Coleta_de_dados_atualizada_emenda.pdf	21/05/2019 09:44:09	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA_CEP_emenda.pdf	21/05/2019 09:42:20	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_PARA_APRESENTACAO_E_JUSTIFICATIVA_PARA_EMENDA_AO_PROJETO.pdf	21/05/2019 09:40:48	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_ORIENTACAO.pdf	28/08/2018 13:58:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_COMPROMISSO.pdf	28/08/2018 13:58:05	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_CONFIDENCIALIDADE.pdf	28/08/2018 13:57:49	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	TERMO_RESPONSABILIDADE.pdf	28/08/2018 13:57:06	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_EMENDA_ELAINE.pdf	28/08/2018 13:54:52	FRANCELISE BRIDI CAVASSIN	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_PESQUISA2.pdf	29/05/2018 16:23:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa_2.pdf	29/05/2018 16:21:47	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	CARTA_RESPOSTA_A_PENDENCIA.pdf	29/05/2018 16:20:01	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Declaracao_do_orientador_do_aluno.pdf	14/04/2018 11:18:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Carta_de_encaminhamento.pdf	14/04/2018 11:17:21	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Confidencialidade.pdf	14/04/2018 11:16:35	FRANCELISE BRIDI CAVASSIN	Aceito

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Outros	Declaracao_de_tornar_publico_os_resultados.pdf	14/04/2018 11:15:48	FRANCELISE BRIDI CAVASSIN	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Uso_de_material_ou_dados.pdf	14/04/2018 11:14:15	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Compromisso_de_utilizacao_de_dados.pdf	14/04/2018 11:12:42	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Termo_de_Responsabilidade.pdf	14/04/2018 11:10:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Instrumento_de_Pesquisa.pdf	14/04/2018 11:09:57	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Qualificacao_dos_pesquisadores.pdf	14/04/2018 11:08:50	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Laboratorio.pdf	14/04/2018 11:07:35	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Concordancia_Farmacia.pdf	14/04/2018 11:06:31	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Ausencia_de_Custos.pdf	14/04/2018 11:05:26	FRANCELISE BRIDI CAVASSIN	Aceito
Outros	Check_List.pdf	14/04/2018 11:04:09	FRANCELISE BRIDI CAVASSIN	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_do_termo_de_consentimento.pdf	14/04/2018 10:59:20	FRANCELISE BRIDI CAVASSIN	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 06 de Setembro de 2020

Assinado por:
Miguel Roberto Jorge
(Coordenador(a))