

Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

April 2009

Safety and Efficacy of Lipid-based Amphotericin B

Discussants



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Abstract

Invasive fungal infections are an important cause of morbidity and mortality in critically ill and immunocompromised patients. Amphotericin B has remained the gold standard treatment for systemic fungal infections. The primary obstacle to amphotericin B therapy is its poor solubility and dose-related toxicities, especially renal impairment. As a result, newer lipid-based formulations of amphotericin B have been developed. This monograph compares available pharmacokinetic, efficacy, and safety data for the 3 lipid-based formulations of amphotericin B, with reference to various patient populations. Potential causes of infusion-related reactions are described, and a premedication algorithm for the prevention of infusion-related reactions is developed.

Efficacy and Pharmacokinetics of Lipid-based Amphotericin B Formulations

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Invasive fungal infections are an important cause of morbidity and mortality in critically ill and immunocompromised patients, including cancer patients receiving intensive chemotherapy regimens and those undergoing hematopoietic stem cell transplantation. The broad-spectrum antifungal agent amphotericin B is a polyene antibiotic that was introduced into therapy in 1957.¹ For decades, amphotericin B has remained the gold standard treatment for systemic fungal infections. Historically, the primary mechanism of action attributed to amphotericin B was its interaction with ergosterol within the fungal cell membrane; 8 molecules of amphotericin B can interact with 8 molecules of ergosterol (cholesterol in mammalian cells). This interaction leads to the development of pores with an aqueous core. Two of such pores form a channel through which fungal cell components leak out, disrupting osmotic integrity and causing cell death.^{2,3} Inhibition of the proton-ATPase in the fungal cell membrane (of the sodium-potassium-ATPase in mammalian cells) and lipid-peroxidation are additional cytotoxic mechanisms.⁴

Acquired resistance to amphotericin B hardly ever occurs.⁵ Instead, the primary obstacle to amphotericin B therapy is its dose-related toxicity, comprising infusion-related adverse effects such as nausea and chills as well as renal impairment.⁶ To circumvent these drawbacks, newer lipid-based formulations of amphotericin B have been developed. Currently, there are 3 lipid formulations available: the lipid complex Abelcet® (Enzon Pharmaceuticals), the liposomal AmBisome® (Astellas Pharma), and the cholesteryl sulfate-stabilized colloidal complex AMPHOTEC/AMPHOCIL® (Three Rivers Pharmaceuticals/Torrex Chiesi Pharma).

Efficacy of Lipid-based Amphotericin B Agents for Invasive Fungal Infections

The general goal of the development of lipid-based amphotericin B formulations is to reduce infusion-related reactions (IRRs) and nephrotoxicity. The development and approval of these lipid-based amphotericin B formulations were based on their comparison with conventional amphotericin B in clinical trials.

Abelcet has been evaluated in 3 open-label studies and is licensed for the second-line treatment of systemic fungal infections. A pooled analysis of 473 patients treated in this setting, of whom 282 were evaluable, found that Abelcet was active in patients who were refractory to conventional amphotericin B.⁷ However, several studies have indicated that toxicities associated with Abelcet occur at a higher rate than with Ambisome.⁸⁻¹⁰

Ambisome was found to be as effective as conventional amphotericin B in 2 randomized clinical trials. In a double-blind multicenter trial, 687 patients were randomized to receive either drug as empirical therapy for persistent fever or neutropenia.¹¹ A similar composite rate of treatment success was observed among patients receiving Ambisome and conventional amphotericin B (50% vs 49%) and was not significantly affected by the concomitant administration of colony-stimulating factors. This finding translated to similar outcomes, including survival (93% vs 90%) and fever resolution (58% in each treatment arm). Notably, Ambisome was associated with significantly less toxicity, including infusion-related fever (16.9% vs 43.6%, $P \leq .001$) and chills or rigors (18.4% vs 54.4%, $P \leq .001$). Less than half the patients in the Ambisome arm exhibited elevated serum creatinine levels, indicative of nephrotoxicity (12% vs 26%, $P < .001$).

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Funding for this Clinical Roundtable Monograph has been provided through an educational grant from Three Rivers Pharmaceuticals/Torrex Chiesi Pharma. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc, the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

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Ambisome was also evaluated in a subsequent double-blind study, in which it was instead compared with Abelcet for the empirical treatment of febrile neutropenia.¹² Importantly, although the 2 lipid formulations were similarly efficacious, Ambisome was associated with significantly less toxicity. These toxicities included infusion-related fever (19.8% vs 57.7%, $P < .001$), chills or rigors (23.5% vs 79.5%, $P < .001$), and nephrotoxicity (14.8% vs 42.3%, $P < .01$). As a result, fewer patients receiving Ambisome discontinued therapy due to toxicity (12.3% vs 32.1%, $P = .004$).¹² As a result of its performance in clinical trials, Ambisome is currently licensed for the empirical treatment of febrile, neutropenic patients in whom a fungal infection is suspected, as well as first- and second-line therapy for various systemic fungal infections.¹³

Several clinical trials evaluated the efficacy of Amphotec/Amphocil compared with conventional amphotericin B. In a retrospective review, 82 patients with aspergillosis who had received Amphotec/Amphocil in a clinical trial setting were compared with 261 aspergillosis patients treated with conventional amphotericin B.¹⁴ Although baseline characteristics were relatively well balanced between the 2 groups, patients who received Amphotec/Amphocil were more likely to have a preexisting renal impairment (40.7% vs 8.7%) and neutropenia at baseline (42.5% vs 15.9%). In this retrospective study, rate of response (48.8% vs 23.4%, $P < .001$) and survival (50% vs 28.4%, $P < .001$) were higher in patients treated with Amphotec/Amphocil compared with conventional amphotericin B. The higher efficacy of Amphotec/Amphocil occurred with a concomitant decrease in renal dysfunction (8.2% vs 43.1%, $P < .001$; relative risk [RR], 0.13). Following this, a randomized double-blind study was conducted to compare Amphotec/Amphocil with standard amphotericin B in the empirical treatment of fever and neutropenia.¹⁵ A total of 213 patients were randomized to receive either drug after at least 3 days of empirical antibiotic therapy for the same symptoms. In this study, a statistically similar rate of response was observed between the 2 treatment arms (50% vs 43.2% in Amphotec/Amphocil vs amphotericin B, respectively). Amphotec/Amphocil treatment resulted in renal dysfunction in a smaller proportion of patients compared with amphotericin B ($P < .001$). However, other toxicities, including infusion-related hypoxia and chills, occurred more frequently with Amphotec/Amphocil treatment. More recently, a randomized multicenter trial evaluated the efficacy and safety of Amphotec/Amphocil compared with amphotericin B in the treatment of invasive aspergillosis occurring in 174 immunocompromised patients.¹⁶ Again, the efficacy of Amphotec/Amphocil was comparable to amphotericin B in this study, producing statistically similar rates of response (52% vs 51%), mortality (36% vs 45%), and fungal infection-associated death (32% vs 26%). This study also showed significantly reduced rates of nephrotoxicity (25% vs 49%, $P = .002$) and a longer median time to the onset of renal toxicity (301 vs 22 days, $P < .001$).

Differences in Pharmacokinetics of the Lipid-based Amphotericin B Agents

For conventional amphotericin B, the mean drug half-life is approximately 24 hours; the mean peak drug concentration (C_{max}) is 1–2 mg/L after a dose of 1 mg/kg, and the mean apparent volume of distribution (V_d) is approximately 2 L/kg.¹⁷ Because of its infusion-related toxicity, the infusion time should amount to at least 4 hours. Among the lipid-based formulations of amphotericin B, Ambisome (standard dose: 3 mg/kg/day) achieves the highest C_{max} (~30 mg/L, infusion time 1 hour) compared with Amphotec/Amphocil (standard dose: 3–4 mg/kg/day; C_{max} : 2.8 mg/L after 4 mg/kg at steady state) and Abelcet (standard dose: 5 mg/kg/day; C_{max} : 1.7 mg/L).^{17,18} However, Abelcet displays the longest half-life (173 hours) compared with Amphotec/Amphocil (32 hours)¹⁸ and Ambisome (6.3 hours).^{18,19} The V_d of each lipid formulation corresponds with the half-life rankings (~130, ~4, and ~0.2 L/kg for Abelcet, Amphotec/Amphocil, and Ambisome, respectively).¹⁷ The diversity of the pharmacokinetic parameters of each of these lipid formulations is quite apparent, and researchers face the question: if this is true, why are the biologic activity and clinical efficacy of these lipid-based formulations, as well as conventional amphotericin B, so similar?^{20,21}

To answer this question, a high-performance liquid chromatography assay was developed to distinguish between the lipid-bound and -liberated fractions of Ambisome and Amphotec/Amphocil within the blood plasma.²² Using this assay, the pharmacokinetic differences were found to be even more pronounced in the lipid-bound fractions, whereas only relatively minor differences were observed between the lipid-liberated fractions.²¹ These data suggest that the lipid-liberated fraction of the amphotericin B formulation is the active component. These results were also confirmed in patients undergoing renal venous filtration, further demonstrating that this procedure does not significantly affect the pharmacokinetics of these lipid formulations.^{23,24}

Postmortem studies have been performed to determine the tissue concentrations of the various formulations of amphotericin B. In one study of 13 patients who died after receiving conventional amphotericin B, only a small proportion of the drug was found to be diffusible and bioactive.²⁵ The total dose of amphotericin B recovered from each organ was 27.5% in the liver, 5.2% in the spleen, 3.2% in the lungs, and 1.5% in the kidneys, suggesting excretion in the bile as a primary mechanism. A more recent autopsy study of 20 patients who died from multiorgan failure determined the tissue concentrations of Ambisome and Amphotec/Amphocil.²⁶ This study also found the highest concentrations of amphotericin B in the liver and spleen. Intermediate concentrations were recorded in the kidneys and the lungs, lower levels in the myocardium and brain. Interestingly, concentrations in the kidneys and lungs were 3-fold higher in patients treated with Amphotec/Amphocil

compared with Ambisome ($P=.018$ and $P=.010$ for kidney and lung comparisons, respectively).²⁶ Despite the differences observed in these studies, it is still not established if the variation in tissue concentrations has an impact on clinical efficacy, because of a lack of comparative data. There have been clinical investigations to compare the nephrotoxicity of conventional amphotericin B and Amphotec/Amphocil, respectively.^{15,16} Results from these studies suggest that the incidence of nephrotoxicity is comparable with that of Ambisome, whereas renal damage occurs more frequently with Abelcet therapy.^{12,27,28}

It is also apparent that very little lipid-encapsulated amphotericin B can penetrate pleural effusion. In one study of 7 critically ill patients who received various lipid-based amphotericin B formulations, the drug was found at concentrations of only 0.02–0.43 mg/mL within pleural effusion samples, suggesting a penetration ratio between 3–44% of the respective plasma concentration.²⁹ Penetration of amphotericin B into ascites is also poor.³⁰ Administration of lipid formulations achieved somewhat higher levels (0.22–0.34 mg/L) in this compartment than conventional amphotericin B.³¹

Recently, amphotericin B concentrations achieved within different intrapulmonary compartments have been investigated in an animal model. Whereas amphotericin B concentrations in whole lung tissue were similar to those in human autopsy samples, markedly lower amounts could be recovered from epithelial lining fluid.³²

Taken together, these studies indicate there are pharmacokinetic differences between the lipid formulations of amphotericin B.^{17,33} In the plasma, the highest levels are achieved by Ambisome, intermediate concentrations are achieved by Amphotec/Amphocil, whereas the lowest concentrations are reached by Abelcet. These differences are likely due to variations of the concentrations of the lipid encapsulated fraction of each drug. Small studies suggest differences in the penetration into the total lung tissue, where Amphotec/Amphocil achieves the highest concentrations compared with Ambisome or conventional amphotericin B. However, whether this observation has any significant clinical impact is still unknown.

References

1. Utz JR, Treger A, McCullough NB, Emmons CW. Amphotericin B: intravenous use in 21 patients with systemic fungal diseases. *Antibiot Annu.* 1958-1959;6:628-634.
2. De Kruijff B, Demel RA. Polyene antibiotic-sterol interactions in membranes of *Acholeplasma laidlawii* cells and lecithin liposomes. 3. Molecular structure of the polyeneantibiotic-cholesterol complexes. *Biochim Biophys Acta.* 1974 26;339:57-70.
3. Baginski M, Resat H, McCammon JA. Molecular properties of amphotericin B membrane channel: a molecular dynamics simulation. *Mol Pharmacol.* 1997 52;560-570.
4. Brajtburg J, Bolard J. Carrier effects on biological activity of amphotericin B. *Clin Microbiol Rev.* 1996 9;512-531.
5. Barker KS, Rogers PD. Recent insights into the mechanisms of antifungal resistance. *Curr Infect Dis Rep.* 2006;8:449-456.
6. Saliba F, Dupont B. Renal impairment and amphotericin B formulations in patients with invasive fungal infections. *Med Mycol.* 2008;46:97-112.
7. Enzon Pharmaceuticals Inc. Abelcet prescribing information. Available online: <http://www.enzon.com/company/abelcet-feb-2009.pdf>. Accessed February 1, 2009.
8. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A; L Amph/ABLC Collaborative Study Group. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Infect Dis.* 2000;31:1155-1163.
9. Fleming RV, Kantarjian HM, Husni R, Rolston K, Lim J, Raad I, Pierce S, Cortes J, Estey E. Comparison of amphotericin B lipid complex (ABLC) vs. ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. *Leuk Lymphoma.* 2001;40:511-520.
10. Hachem RY, Boktour MR, Hanna HA, et al. Amphotericin B lipid complex versus liposomal amphotericin B monotherapy for invasive aspergillosis in patients with hematologic malignancy. *Cancer.* 2008;112:1282-1287.
11. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med.* 1999;340:764-771.
12. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Infect Dis.* 2000;31:1155-1163.
13. Astellas Pharma US Inc. Ambisome prescribing information. Available online: <http://www.astellas.us/docs/Ambisome.pdf>. Accessed February 1, 2009.
14. White MH, Anaissie EJ, Kusne S, et al. Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis. *Clin Infect Dis.* 1997;24:635-642.
15. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. *Clin Infect Dis.* 1998;27:296-302.
16. Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis.* 2002;35:359-366.
17. Bellmann R. Clinical pharmacokinetics of systemically administered antimycotics. *Curr Clin Pharmacol.* 2007;2:37-58.
18. Amantea MA, Bowden RA, Forrest A, Working PK, Newman MS, Mamelok RD. Population pharmacokinetics and renal function-sparing effects of amphotericin B colloidal dispersion in patients receiving bone marrow transplants. *Antimicrob Agents Chemother.* 1995;39:2042-2047.
19. Adedoyin A, Bernardo JF, Swenson CE, et al. Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. *Antimicrob Agents Chemother.* 1997;41:2201-2208.
20. Frothingham R. Lipid formulations of amphotericin B for empirical treatment of fever and neutropenia. *Clin Infect Dis.* 2002 35;896-897
21. Bellmann R, Egger P, Wiedermann CJ. Differences in pharmacokinetics of amphotericin B lipid formulations despite clinical equivalence. *Clin Infect Dis.* 2003;36:1500-1501.
22. Egger P, Bellmann R, Wiedermann CJ. Determination of amphotericin B, liposomal amphotericin B, and amphotericin B colloidal dispersion in plasma by high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl.* 2001;760:307-313.
23. Bellmann R, Egger P, Gritsch W, et al. Amphotericin B lipid formulations in critically ill patients on continuous veno-venous haemofiltration. *J Antimicrob Chemother.* 2003;51:671-681.
24. Bellmann R, Egger P, Djanani A, Wiedermann CJ. Pharmacokinetics of amphotericin B lipid complex in critically ill patients on continuous veno-venous haemofiltration. *Int J Antimicrob Agents.* 2004;23:80-83.
25. Collette N, van der Auwera P, Lopez AP, Heymans C, Meunier F. Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. *Antimicrob Agents Chemother.* 1989;33:362-368.
26. Vogelsinger H, Weiler S, Djanani A, et al. Amphotericin B tissue distribution in autopsy material after treatment with liposomal amphotericin B and amphotericin B colloidal dispersion. *J Antimicrob Chemother.* 2006;57:1153-1160.
27. Fleming RV, Kantarjian HM, Husni R, et al. Comparison of amphotericin B lipid complex (ABLC) vs. ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. *Leuk Lymphoma.* 2001;40:511-520.
28. Hachem RY, Boktour MR, Hanna HA, et al. Amphotericin B lipid complex versus liposomal amphotericin B monotherapy for invasive aspergillosis in patients with hematologic malignancy. *Cancer.* 2008;112:1282-1287.
29. Weiler S, Bellmann-Weiler R, Joannidis M, Bellmann R. Penetration of amphotericin B lipid formulations into pleural effusion. *Antimicrob Agents Chemother.* 2007;51:4211-4213.
30. van der Voort PH, Boerma EC, Yska JP. Serum and intraperitoneal levels of amphotericin B and flucytosine during intravenous treatment of critically ill patients with *Candida* peritonitis. *J Antimicrob Chemother.* 2007; 59: 952-956.
31. Weiler S, Bellmann-Weiler R, Dunzendorfer S, Joannidis M, Bellmann R. Levels of amphotericin B lipid formulations in ascites. *J Antimicrob Chemother.* 2008;62:1163-1164.
32. Groll AH, Lyman CA, Petraitis V, et al. Compartmentalized intrapulmonary pharmacokinetics of amphotericin B and its lipid formulations. *Antimicrob Agents Chemother.* 2006;50:3418-3423.
33. Dodds Ashley ES, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. *Clin Infect Dis.* 2006;43:S28-S39.

Safety of Amphotericin B Formulations

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Use of Amphotericin B in Different Patient Populations

Currently, amphotericin B could be considered the treatment of choice not only for adults with systemic fungal infections, but for pediatric patients as well.¹ In children, its use is usually limited to cancer patients with established or suspected fungal infections and as prophylaxis for immunosuppressed patients. Many children with malignant diseases who are admitted with fever receive empiric amphotericin B therapy when the fever persists, despite adequate antibiotics to prevent fungal superinfection and to control clinical or subclinical fungal infection. Neonates especially may benefit from amphotericin B formulations.² Only limited clinical research exists for the use of conventional amphotericin B in neonates, and dosage recommendations are based on those used in adults. The same is also true for the liposomal formulations of amphotericin B as well.³ However, the existing data show that both conventional and lipid formulations are active in pediatric and neonatal patients. In one study of 56 infants with systemic candidiasis, 52 of whom were preterm, there was no significant difference in the rate of mortality between those who received conventional amphotericin B versus those who received Amphotec/Amphocil or Ambisome.⁴ There was also no significant difference in the resolution of infection among these 3 agents (67.6%, 57.1%, and 83.3% in patients receiving conventional amphotericin B, Amphotec/Amphocil, or Ambisome, respectively). In a separate open-label clinical trial, Abelcet was reported to produce a complete or partial therapeutic response in 70% of pediatric patients with aspergillosis or candidiasis.⁵ These results were supported in a retrospective study that reported a therapeutic response rate of 83%.⁶ Because of the similarity in activity among these various amphotericin B agents, the selection of the appropriate amphotericin B formulation is recently based not on efficacy, but mainly on the potential of nephrotoxicity or IRR.

Cancer patients form a significant, immunocompromised population at risk for systemic fungal infections.⁷ Several risk factors predispose cancer patients for an increased risk of developing an invasive fungal infection, including a history or a previous fungal infection, prolonged neutropenia (>10 days), older age, use of broad spectrum antibiotics, treatment with corticosteroids, and active cancer.⁸ In addition to its empirical and directed uses as an antifungal agent, amphotericin B is administered as chemoprophylaxis and as a preemptive agent.

Safety Profile of Lipid-based Amphotericin B Agents

The use of conventional amphotericin B is limited primarily by substantial toxicity that is either renal- or infusion-related.^{10,11} Though the use of Amphotec/Amphocil is associated with an improvement in renal-related toxicities, infusion-related toxicities are quite apparent. The renal safety profile of Amphotec/Amphocil is still acceptable even in the pediatric population. In fact, a recent study showed that Amphotec/Amphocil could be considered the treatment of choice, due to a decreased occurrence of late renal toxicity compared with other formulations. In this case, late renal toxicity is defined as occurring over 3 years after entering remission, and toxicity is determined by measuring tubular and glomerular function. Although treatment with conventional amphotericin B is associated with an increased risk of late renal toxicity, this is not the case for patients treated with Amphotec/Amphocil, with adequate hydration and Na⁺ and K⁺ supplementation. However, although renal toxicity seems to be improved with this formulation and the aforementioned measures, IRRs still remain a significant issue.

Possible Causes of Infusion-related Reactions

Increasingly, research suggests that the induction of inflammatory cytokines and their release is a major mechanism by which amphotericin B induces IRRs.¹²⁻¹⁶ Compared with Abelcet and Amphotec/Amphocil, Ambisome therapy results in the lowest cytokine induction. In that study, the investigators attributed Ambisome's association with the lowest infusion-related toxicity to low cytokine induction.¹⁷ We recently reported results from a clinical study in which we analyzed cytokine release in pediatric patients with cancer treated with different amphotericin B formulations.¹⁸ In these patients, blood samples were taken both prior to infusion (15–30 minutes before infusion), as well as during the third hour of infusion or earlier, during the occurrence of an infusion-related toxicity. Data for both time periods were available for 48 episodes of amphotericin B administration for comparison.

Flow cytometric evaluation of immune system was performed on the level of:

1. lymphocyte subpopulations + human lymphocyte antigen (HLA)-Dr on monocytes; T-helper (CD4) + T-cytotoxic (CD8); T-lymphocyte activation (CD25, HLA-Dr); T-lymphocyte subtypes (naive-CD45RA+, effector CD27); natural killer cells (CD16, CD56);
2. cytokines level—multiplex bead-based array—11-plex analyzing interleukin (IL)-12p70, interferon-gamma, IL-2, tumor necrosis factor (TNF)-beta, IL-10, IL-5, IL-4, IL-6, IL-1beta, TNFalpha, and IL-8.

Flow cytometry showed significant differences in the relative numbers of immune system cells.¹⁸ For example, compared with patients who did not experience an infusion-related toxicity, those who experienced Amphotec/Amphocil infusion-related toxicities exhibited significantly increased levels of CD4+RO+27 (memory helpers). Analysis of the blood samples revealed significant changes in the cytokine profiles of patients before and during Amphotec/Amphocil administration.¹⁸ Levels of IL-6, an inflammatory cytokine released by stimulated T cells, were significantly increased in patients who experienced infusion-related toxicities, especially among patients who experienced shivers as a symptom. These data suggested that IL-6 may have an important role in determining Amphotec/Amphocil infusion-related toxicity. Similarly, levels of IL-8 also were significantly increased, although not to the same extent as IL-6. Conversely, no significant changes were observed in IL-1b, which has been suggested to be involved in the development of infusion-related toxicity.¹⁹ This is concurrent with another recent study, which also reported a nonsignificant increase in IL-1b levels.²⁰ Our data may stimulate further research towards to rationally designed premedication practice.

References

- Goldman RD, Koren G. Amphotericin B nephrotoxicity in children. *J Pediatr Hematol Oncol*. 2004;26:421-426.
- Filiori I, Iosifidis E, Roilides E. Therapeutic strategies for invasive fungal infections in neonatal and pediatric patients. *Expert Opin Pharmacother*. 2008;9:3179-3196.
- Almirante B, Rodriguez D. Antifungal agents in neonates: issues and recommendations. *Paediatr Drugs*. 2007;9:311-321.
- Linder N, Klinger G, Shalit I, et al. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. *J Antimicrob Chemother*. 2003;52:663-667.
- Walsh TJ, Seibel NL, Arndt C, et al. Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J* 1999;18:702-708.
- Herbrecht R, Auvrignon A, Andres E, et al. Efficacy of amphotericin B lipid complex in the treatment of invasive fungal infections in immunosuppressed paediatric patients. *Eur J Clin Microbiol Infect Dis*. 2001;20:77-82.
- Bohme A, Ruhnke M, Buchheidt D, et al. Treatment of invasive fungal infections in cancer patients—recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol*. 2009;88:97-110.
- Staber P, Langner S, Dornbusch HJ, Neumeister P. Antifungal management in cancer patients. *Wien Med Wochenschr*. 2007;157:503-510.
- Pappas PG, Kauffman CA, Andes D, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:503-35.
- Barrett JP, Vardulaki KA, Conlon C, et al. A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. *Clin Ther*. 2003;25:1295-1320.
- Ellis D. Amphotericin B: spectrum and resistance. *J Antimicrob Chemother*. 2002;49 Suppl 1:7-10.
- Ghezzi MC, Raponi G, Filadoro F, Mancini C. The release of TNF-alpha and IL-6 from human monocytes stimulated by filtrates of *Candida albicans* after treatment with amphotericin B. *J Antimicrob Chemother*. 1994;33:1039-1043.
- Sau K, Mambula SS, Latz E, Henneke P, Golenbock DT, Levitz SM. The antifungal drug amphotericin B promotes inflammatory cytokine release by a Toll-like receptor- and CD14-dependent mechanism. *J Biol Chem*. 2003;278:37561-37568.
- Turtinen LW, Prall DN, Bremer LA, Nauss RE, Hartsel SC. Antibody array-generated profiles of cytokine release from THP-1 leukemic monocytes exposed to different amphotericin B formulations. *Antimicrob Agents Chemother*. 2004;48:396-403.
- Turtinen LW, Bremer LA, Prall DN, Schwartzhoff J, Hartsel SC. Distinct cytokine release profiles from human endothelial and THP-1 macrophage-like cells exposed to different amphotericin B formulations. *Immunopharmacol Immunotoxicol*. 2005;27:85-93.
- Simitsopoulou M, Roilides E, Dotis J, et al. Differential expression of cytokines and chemokines in human monocytes induced by lipid formulations of amphotericin B. *Antimicrob Agents Chemother*. 2005;49:1397-1403.
- Arning M, Kliche KO, Heer-Sonderhoff AH, Wehmeier A. Infusion-related toxicity of three different amphotericin B formulations and its relation to cytokine plasma levels. *Mycoses*. 1995;38:459-465.
- Sterba J. Persistent fever and neutropenia in a child: infusion-related toxicity "fear factor"? Presented at: 5th Amphocil Family Meeting, Verona, Italy, November 15, 2008.
- McGuire TR, Tricker WJ, Smith L, Hoie EB, Miller DW. Release of TNF-alpha and IL-1beta from porcine brain endothelium corresponds to the pyrogenic potential of three marketed formulations of amphotericin. *Inflamm Res*. 2005;54:375-379.
- Pai MP, Norenberg JP, Telepak RA, Sidney DS, Yang S. Assessment of effective renal plasma flow, enzymuria, and cytokine release in healthy volunteers receiving a single dose of amphotericin B desoxycholate. *Antimicrob Agents Chemother*. 2005;49:3784-3788.

Management of Infusion-related Reactions

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Species of *Candida* are the most common pathogen that causes systemic fungal infection.¹⁻³ Since the early 1980s, the mortality attributable to *Candida* infection may be as high as 42%, emphasizing the seriousness of this infection. Even with the use of optimal therapy within the United States and Europe, mortality may be over 20%. In addition, invasive fungal infections, new resistance patterns, and resistance to new antifungal therapies continue to be troublesome. These observations, coupled with the fact that amphotericin B is still the gold standard therapeutic despite its approval over 50 years ago, demonstrate that a need remains for pharmacologic improvements in therapy. Additionally, improvements resulting in increased safety are an important strategy, as there are only a very few new agents that offer improved microbial benefit over the current therapies.

Causes of Amphotericin B Infusion-related Reactions

In order to use the best treatment strategy for IRRs, it is first important to understand the mechanism behind the development of these reactions. In 1987, Gigliotti and colleagues first proposed that the induction of prostaglandin synthesis was responsible for amphotericin B IRRs.⁴ They further showed that pre-administration with ibuprofen, an inhibitor of prostaglandin synthesis, reduced the incidence of the chills that are frequently associated with these IRRs (from 87% to 49%, $P=.01$).⁵ However, despite the potential benefit of including a nonsteroidal anti-inflammatory drug, these are themselves associated with a risk of renal toxicity.⁶ For this reason, the use of ibuprofen is discouraged in patients requiring amphotericin B therapy, as this is likely to increase vasoconstriction of the kidney arteries, leading to renal dysfunction.

Following the initial research that suggested prostaglandin synthesis the main mechanism in amphotericin B IRRs, subsequent studies found that this prostaglandin synthesis occurred only secondary to amphotericin B-induced release of inflammatory cytokines.^{7,8} These inflammatory cytokines include IL-1 β , -6, and tumor necrosis factor.⁹⁻¹¹ Activation of the immune system and the resulting cytokine release are probably related to the enhanced clinical effect of amphotericin B as an antifungal agent.¹² Thus, it seems that amphotericin B IRRs may be a by-product of the cytokine release and immune system stimulation. Hypertension is a rarely reported side effect of amphotericin B formulations. However, hypotension is common; cytokines or immune stimulation appear to be the primary mechanism for the reaction.^{13,14} Interestingly, differences in IRRs among patients may be due to variations in their expression of these cytokines. More research is required to determine these genotypic and phenotypic variations, and to assess if they are associated with an increased risk or severity of IRRs. It is possible that in the future, biomarkers may be available to select patients with an increased likelihood for developing IRRs, in order to more optimally administer premedication. Diphenhydramine has not been demonstrated to be beneficial in these patients.

Clinical Data Regarding Premedication Practices for Infusion-Related Reactions

Understanding the mechanism behind amphotericin B IRRs is an important step in order to best address, both pharmacologically and mechanistically, how to prevent them. Targeting the mechanism of cytokine release may be one way to reduce these IRRs. Research has now clearly demonstrated that amphotericin B increases the transcription and translation of the inflammatory cytokines.¹⁵ Studies from the early 1960s first showed that hydrocortisone could be effective in the prevention of amphotericin B IRRs,^{16,17} as corticosteroids are known to inhibit cytokine transcription.¹⁸

Opioid analgesics were also found to be effective in ameliorating IRRs. A report in 1980 first demonstrated in a randomized placebo-controlled trial that the opioid analgesic meperidine hydrochloride significantly reduced the duration of IRRs, reducing the mean cessation time from 37.4 to 10.8 minutes.¹⁹ In this setting, meperidine is generally administered through intravenous bolus.

Mechanistically, adjusting the rate of amphotericin B infusion has also been evaluated to reduce adverse reactions; however, in some populations, there are great risks associated with short infusions. An early study that compared a 2-hour infusion rate with 45 minutes showed that the rapid infusion produced similar rates and severity of adverse reactions.²⁰

Data from the Patient Registry of Amphotericin B Cholesteryl Sulfate Complex for Injection Clinical Tolerability (PRoACT) registry was recently reported, suggesting that

IRRs occurred at a lower rate than previously thought.²¹ PRoACT is a multicenter, worldwide registry which included 170 patients (median age, 37 years) administered a total of 1,230 Amphotec infusions. Of these, 89.8% had premedication, which most frequently included corticosteroids, antihistamines, and acetaminophen. The overall rate of IRRs was 12%; premedication significantly reduced the rate of adverse reactions (11% vs 22%, respectively, $P < .001$). Notably, corticosteroids were significantly associated with a decreased incidence of IRRs. Following premedicated infusions, the incidence of IRRs decreased by approximately half from day 1 to day 2 (31.5% to 15.6%), and by another 58% from day 2 to day 3 (15.6% to 6.5%). Importantly, PRoACT is the first demonstration that the use of corticosteroids in this patient population does not significantly impact mortality. The study reported a trend towards lower mortality among patients who received a corticosteroid as premedication compared with those who did not (21.9% vs 35.7%, $P = .07$). This finding is especially noteworthy, considering prior studies have suggested corticosteroids increase the risk of mortality in patients with invasive fungal infections.²²⁻²⁵ Although the wide variety of antihistamines used in the PRoACT registry made it difficult to perform a meaningful analysis in this small number of patients, the results suggested that this class of drugs did not appear effective as a premedication for prevention of IRRs. Acetaminophen, which was the most commonly reported drug used for premedication in the PRoACT registry, was not found to be effective for preventing Amphotec/Amphocil IRRs; in fact, a higher incidence of reactions was reported among recipients of acetaminophen than nonrecipients. These data corroborated a previous report, which also showed a lack of effect of acetaminophen as a premedication.²⁶ Overall, data from the PRoACT registry may prove useful to set the foundation for a randomized, controlled clinical trial in the future.

A Premedication Algorithm for the Prevention of Amphotec/Amphocil Infusion-related Reactions

Based on research and various clinical trials reported in the literature, several important factors should be considered to abrogate IRRs. Taken together, these can be used to formulate a treatment algorithm for the prevention of IRRs (Figure 1). First, the clinician should carefully calculate an accurate dosage for each individual patient, taking into account the severity of the systemic fungal infection. If the patient is critically ill, with a short survival predicted without aggressive intervention, treatment is typically initiated on day 1 with a half-dose of Amphotec/Amphocil. This dose is then doubled on day 2 of therapy. Corticosteroids are the primary choice for premedication and are continued for the first 3–5 days of therapy. This time frame is optimal for prevention of IRRs, which generally occur during the first few days of therapy, without causing suppression of the hypothalamic-

Figure 1. Amphotec/Amphocil Treatment Algorithm.

<p>Administration</p> <ul style="list-style-type: none"> • Dilute Amphotec/Amphocil with 5% dextrose to a final concentration of 0.6 mg/mL. • Administer initial test dose (0.25 mg/kg) immediately after meal, over 0.75–4 hours. • Carefully monitor for infusion-related reactions. • If initial dose is well-tolerated, advance to maximal dose of 3–4 mg/kg/day by day 3–5. • If infusion-related reaction is apparent, treat reaction and use premedication prior to next infusion. <p>Premedication</p> <ul style="list-style-type: none"> • Hydrocortisone (0.7 mg/kg) to treat and prevent chills and fever associated with Amphotec/Amphocil solution may be directly added and should be discontinued within 3–5 days. • Meperidine hydrochloride (25–50 mg) given parenterally to ameliorate chills. • Normal saline (250 mL) to prevent nephrotoxicity, given prior to Amphotec/Amphocil solution. • Heparin (1,000 U) to diminish thrombophlebitis when Amphotec/Amphocil is administered through peripheral veins. <p>Laboratory</p> <ul style="list-style-type: none"> • Perform laboratory evaluations twice weekly over first 4 weeks; once weekly thereafter. • Laboratory evaluations to include hematocrit, reticulocyte count, magnesium, potassium, creatinine, bicarbonate, blood urea nitrogen. • If renal function decreases (serum creatinine increases by 0.5 mg/dL if baseline <1.2 mg/dL or doubles if baseline >1.2 mg/dL), reassess therapy.

The University of Mississippi treatment algorithm differs from US product labeling.

pituitary-adrenal axis. Because there are currently no data suggesting incompatibility, the corticosteroid may be added directly to the Amphotec/Amphocil infusion bag. Opioid analgesics, including morphine and pethidine/meperidine, can also be used to ameliorate chills in patients.

Aside from premedication treatments, the clinician may use several other strategies to limit other adverse reactions when amphotericin B is administered via the peripheral vein; the addition of heparin may help to decrease the occurrence of thrombophlebitis.²⁶ A bolus administration of normal saline prior to antifungal therapy is suggested to ensure adequate hydration and electrolyte balance, to help limit amphotericin B–induced nephrotoxicity.^{27–29} Also, because of the significant risk of nephrotoxicity, the electrolyte concentrations and serum creatinine in patients should be routinely monitored. Hematocrit values are especially important, as it is an indicator of renal dysfunction that is specifically associated with a decrease in erythropoietin, indicative of amphotericin B-related nephrotoxicity.³⁰

References

- Richardson M, Lass-Flörl C. Changing epidemiology of systemic fungal infections. *Clin Microbiol Infect* 2008;14 Suppl 4:5–24.
- Lai CC, Tan CK, Huang YT, Shao PL, Hsueh PR. Current challenges in the management of invasive fungal infections. *J Infect Chemother* 2008;14:77–85.
- Cornely OA. Aspergillus to Zygomycetes: causes, risk factors, prevention, and treatment of invasive fungal infections. *Infection* 2008;36:296–313.
- Gigliotti F, Shenep JL, Lott L, Thornton D. Induction of prostaglandin synthesis as the mechanism responsible for the chills and fever produced by infusing amphotericin B. *J Infect Dis* 1987;156:784–789.
- Burnett RJ, Reents SB. Premedication for amphotericin B-induced chills. *Clin Pharm* 1989;8:836–837.
- Vonkeman HE, van de Laar MA. Nonsteroidal Anti-Inflammatory Drugs: Adverse Effects and Their Prevention. *Semin Arthritis Rheum* 2008.
- Cleary JD, Chapman SW, Nolan RL. Pharmacologic modulation of interleukin-1 expression by amphotericin B–stimulated human mononuclear cells. *Antimicrob Agents Chemother* 1992;36:977–981.
- Gigliotti F, Shenep JL, Lott L, Thornton D. Induction of prostaglandin synthesis as the mechanism responsible for the chills and fever produced by infusing amphotericin B. *J Infect Dis* 1987;156:784–789.
- Turtinen LW, Bremer LA, Prall DN, Schwartzhoff J, Hartsel SC. Distinct cytokine release profiles from human endothelial and THP-1 macrophage-like cells exposed to different amphotericin B formulations. *Immunopharmacol Immunotoxicol* 2005;27:85–93.
- Turtinen LW, Prall DN, Bremer LA, Nauss RE, Hartsel SC. Antibody array-generated profiles of cytokine release from THP-1 leukemic monocytes exposed to different amphotericin B formulations. *Antimicrob Agents Chemother* 2004;48:396–403.
- Simitsopoulou M, Roilides E, Dotis J, et al. Differential expression of cytokines and chemokines in human monocytes induced by lipid formulations of amphotericin B. *Antimicrob Agents Chemother* 2005;49:1397–1403.
- Ben-Ami R, Lewis RE, Kontoyiannis DP. Immunocompromised hosts: immunopharmacology of modern antifungals. *Clin Infect Dis* 2008;47:226–235.
- Wiwanitkit V. Severe hypertension associated with the use of amphotericin B: an appraisal on the reported cases. *J Hypertens* 2006;24:1445.
- Rodriguez CA, Yamamoto M, Arantes Ade M, Chauffaille Mde L, Colombo AL, Bordin JO. Amphotericin B-induced severe hypertension in a young patient: case report and review of the literature. *Ren Fail* 2006;28:185–187.
- Rogers PD, Stiles JK, Chapman SW, Cleary JD. Amphotericin B induces expression of genes encoding chemokines and cell adhesion molecules in the human monocytic cell line THP-1. *J Infect Dis* 2000;182:1280–1283.
- Saliba A, Beatty OA. Treatment of mycotic infections: hydrocortisone in the control of amphotericin-B toxicity. *Dis Chest* 1962;41:214–219.
- Tynes BS, Utz JP, Bennett JE, Alling DW. Reducing amphotericin B reactions. A double-blind study. *Am Rev Respir Dis* 1963;87:264–268.
- Kovalovsky D, Refojo D, Holsboer F, Arzt E. Molecular mechanisms and Th1/Th2 pathways in corticosteroid regulation of cytokine production. *J Neuroimmunol* 2000;109:23–29.
- Burks LC, Ainsler J, Fortner CL, Wiernik PH. Meperidine for the treatment of shaking chills and fever. *Arch Intern Med* 1980;140:483–484.
- Cleary JD, Weisdorf D, Fletcher CV. Effect of infusion rate on amphotericin B-associated febrile reactions. *Drug Intell Clin Pharm* 1988;22:769–772.
- Paterson DL, David K, Mrsic M, et al. Pre-medication practices and incidence of infusion-related reactions in patients receiving AMPHOTEC: data from the Patient Registry of Amphotericin B Cholesteryl Sulfate Complex for Injection Clinical Tolerability (PROACT) registry. *J Antimicrob Chemother* 2008;62:1392–1400.
- Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *Lancet* 2003;362:1828–1838.
- Dvorak CC, Steinbach WJ, Brown JM, Agarwal R. Risks and outcomes of invasive fungal infections in pediatric patients undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2005;36:621–629.
- Cordonnier C, Ribaud P, Herbrecht R, et al. Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers. *Clin Infect Dis* 2006;42:955–963.
- Hebart H, Bokemeyer C, Löffler J, et al. Management of invasive fungal infections in oncological patients. *Onkologie* 1999;22:192–197.
- Goodwin SD, Cleary JD, Walawander CA, Taylor JW, Grasela TH, Jr. Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis* 1995;20:755–761.
- Echevarria J, Seas C, Cruz M, et al. Oral rehydration solution to prevent nephrotoxicity of amphotericin B. *Am J Trop Med Hyg* 2006;75:1108–1112.
- Girmenia C, Cimino G, Di Cristofano F, Micozzi A, Gentile G, Martino P. Effects of hydration with salt repletion on renal toxicity of conventional amphotericin B empirical therapy: a prospective study in patients with hematological malignancies. *Support Care Cancer* 2005;13:987–992.
- Anderson CM. Sodium chloride treatment of amphotericin B nephrotoxicity. Standard of care? *West J Med* 1995;162:313–317.
- Lin AC, Goldwasser E, Bernard EM, Chapman SW. Amphotericin B blunts erythropoietin response to anemia. *J Infect Dis* 1990;161:348–351.