

Bon Secours Richmond Health System
Pharmacy & Therapeutics Committees
Lipid Amphotericin B Products
1/2003

Recommendations:

- Amphotericin B liposome (AmBisome) and amphotericin B lipid complex (Abelcet) are recommended for formulary inclusion at this time.
- Infectious disease physician input will be requested in selecting one lipid product as the preferred formulation as there is large cost difference between the products.

Findings:

- *Candida* spp. and *Aspergillus* spp are the most commonly encounter fungal pathogens in neutropenic and bone marrow transplantation patients. *Cryptococcus neoformans* causes invasive most commonly in AIDS patients.
- Fungal infections account for 20-30% of fatal infections in patients with acute leukemia, 10-15% of fatal infections in patient with lymphoma, and 5% of fatal infections in patient with solid tumors.
- The frequency of fungal infections among transplant patients ranges from 0-20% for kidney and bone marrow transplants to 10-30% for heart and 30-40% for liver transplant patients.
- 2-4% of all hospitalized patients develop nosocomial infections, with bacteria being most common etiologic agent. Fungi, account for 10% of all blood stream isolates. *Candida* spp., primarily *C. albicans*, is the 4th most common bloodstream isolate with *Candida albicans* accounting for 78% of all nosocomial fungal infections.
- Antifungal therapy in patients receiving chemotherapy therapy is directed primarily at the prevention/treatment of *Candida* and *Aspergillus* infections.
- Nephrotoxicity due to amphotericin is dose related. (Decrease GFR, loss of urinary concentrating ability, renal loss of sodium and potassium, and renal tubular acidosis). Nephrotoxicity is reduced with lipid products.
- Amphotericin B related fever and shaking decreases with subsequent doses and may be pretreated with diphenhydramine, acetaminophen, meperidine, and hydrocortisone.
- Amphotec (amphotericin B cholesteryl sulfate colloid dispersion) has a higher rate of acute severe infusion related reactions than other lipid products, but the reaction rate decline from 35% on day 1 to 14% on day seven.
- High doses of Abelcet (amphotericin b lipid complex) increase tissue concentrations without a concomitant increase in kidney concentrations.
- Amphotericin B liposome (AmBisome) has a slower uptake into reticuloendothelially system as compared to Amphotec and Abelcet.
- Amphotericin B displays concentration dependent killing and may be fungistatic or fungicidal depending on the organism and concentration.
- Major indications for Amphotericin B are invasive candidiasis, cryptococcosis, aspergillosis, blastomycosis, histoplasmosis, coccidioidomycosis, sporotrichosis, and paracoccidioidomycosis. Empiric treatment of choice for febrile neutropenia in patients with poor response to antibacterial agents.
- In vitro correlations with in vivo outcomes in patients are not yet known; the role of routine susceptibility testing is unknown at this time.
- The assay used to measure amphotericin B in the serum after administration of liposomal amphotericin does not distinguish between complexed and uncomplexed amphotericin B.

	Amphotericin B dexocholate Funizone	Amphotericin B Lipid Complex (ABLC) Abelcet	Amphotericin B Liposome L-AMP AmBisome	Amphotericin B Cholesteryl Sulfate Colloid Dispersion (ABCD) Amphotec
Indications	Potentially life-threatening fungal infections: aspergillosis, blastomycosis, systemic candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, and zygomycosis; empiric antifungal therapy in febrile neutropenic patients for suppressive therapy against recurrence or relapse of cryptococcosis, histoplasmosis, coccidioidomycosis; antifungal prophylaxis in certain immunosuppressed individuals	1. Invasive fungal infections in patients refractory to or intolerant to amphotericin B deoxycholate	1. Empiric antifungal therapy in febrile neutropenic patients 3 mg/kg/day 2. Cryptococcal Meningitis in HIV positive patients 6 mg/kg/day 3. Treatment of Aspergillus spp, Candida spp, Cryptococcus infections <i>refractory</i> to Amphotericin B deoxycholate or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B. deoxycholate 3-5 mg/kg/day 4. Treatment of Visceral leishmaniasis	Invasive aspergillosis infections in patients with renal impairment or unacceptable toxicity to amphotericin b deoxycholate or in patients refractory to amphotericin B deoxycholate.
Normal Dose	0.5-1.5 mg/kg/day	5 mg/kg/day	3-6 mg/kg/day	3-4 mg/kg/day
Infusion Rate	Over 4 hours	2.5 mg/kg/hour	Over 2 hours	1 mg/kg/hour
Test dose	Yes	No	No	Yes
Infusion Concentration		1-2 mg/ml		0.16-0.83 mg/ml
Structure	Colloidal suspension	Ribbon 1:1 molar ration 2 phospholipids and amphotericin b	Vesicle (true liposome) (unilamellar liposome)	Disk-like 1:1 molar ratio complex of amphotericin B and cholesteryl sulfate
Dose for Kinetics	0.6 mg/kg/day Data from Abelcet PI	5 mg/kg/day	5 mg/kg/day	4 mg/kg/day
Kinetics	Less than dose proportional Non linear	Less than dose proportional Non linear Steady state Vd and Clearance increase with increasing dosage	Non Linear	Less than dose proportional Non linear Steady state Vd and Clearance increase with increasing dosage
Cmax	1.1 mcg/ml	1.7 mcg/ml	83 mcg/ml	2.9 mcg/ml
Trough	0.4 mcg/ml	0.6 mcg/ml		
AUC	17.1 mcg/ml/h	14 mcg/ml/h	555 mcg/ml/h	36 mcg/ml/h
PO Bioavailability (%)	Nil	NA	NA	NA
Clearance	38 ml/hr/kg	436 ml/hr/kg	11 ml/hr/kg	112 ml/hr/kg
Half-life (hours)	13.7	14.6	6.8 h	
Terminal T1/2	91 h	173 h		28.2 h
% Renally eliminated at 24 hours	9.6% Abelcet PI	0.9% PI		
Renal elimination	Renal 32% after 1 week			
Other routes of elimination	Fecal/Biliary 40% after 1 week			
Protein binding (%)				

VD (L/kg)	5 l/kg	131 l/kg	0.1 l/kg	4.1
	Tissue Concentrations			
Spleen		290 mcg/g		
Lung		222 mcg/g		
Liver		196 mcg/g		
Lymph Node		7.6 mcg/g		
Kidney		6.9 mcg/g		
Heart		5 mcg/g		
Brain		1.6 mcg/g		
Primary route of elimination		Reticuloendothelial system	Reticuloendothelial system	Reticuloendothelial system
Renal Impairment effect on dose		Effect unknown	Effect unknown	Effect unknown
Hepatic Impairment effect on dose		Effect unknown	Effect unknown	Effect unknown
Dialysis effect on dose	Not Removed	Effect unknown	Effect unknown	
Studied In Peds			302 patients	

Abelcet (Amphotericin B Lipid Complex, ABLC) Data from the Package Insert

473 patients were pooled from three open-labels studies in which Abelcet was used in patients with invasive fungal infections. Patients were refractory to or intolerant of conventional amphotericin B or had pre existing nephrotoxicity (scr > 2.5 mg/dl for adults, 1.5 mg/dl for children or clcr < 25 ml/min).

Changes in Mean Serum Creatinine Over Time in Patients with Aspergillosis and Serum Creatinine > 2.5 mg/dl at Baseline		
	Abelcet	Amphotericin b (Historical Controls)
Median Age 39 (years)		
Male 65%		
Mean Difference from Baseline		
Week 1, mg/dl (number of patients)	- 0.1 (49)	0 (38)
Week 2, mg/dl (number of patients)	- 0.6 (24)	- 0.2 (26)
Week 3, mg/dl (number of patients)	- 0.8 (18)	- 0.3 (19)
Week 4, mg/dl (number of patients)	-1.3 (12)	0.15 (12)
Week 5, mg/dl (number of patients)	-1.4(11)	- 0.4 (7)
Week 6, mg/dl (number of patients)	- 1.2 (9)	- 0.5 (6)

Three randomized trials noted below.

Clin Infect Dis 1996 Feb;22(2):315-21

Amphotericin B lipid complex (Abelcet) compared with amphotericin B in the treatment of cryptococcal meningitis in patients with AIDS. Sharkey PK.

(Randomized open labeled)The study objective was to obtain preliminary information regarding the safety and efficacy of amphotericin B (AmB) lipid complex (ABLC) (Abelcet) in the treatment of *AIDS-associated cryptococcal meningitis*. Of 55 patients randomly assigned to 6 weeks of therapy with ABLC (1.2-5.0 mg/kg/day), with ascending doses for three sequential cohorts) or Amphotericin B (0.7-1.2 mg/kg/day), 46 received > or = 12 doses. Transfusion requirements, mean decreases in hemoglobin level, and mean increases in creatinine level were significantly greater with Amphotericin B than with Abelcet. The total number of adverse events, infusion-related events, and occurrences of hypomagnesemia and hypokalemia associated with each form of therapy were similar. Among 21 recipients of ABLC at a dosage of 5 mg/kg (daily for 2 weeks and then thrice weekly for 4 weeks), symptoms and signs resolved for 18 (86%). Of those receiving > or = 12 doses of ABLC, cultures converted to negative for 8 (42%), were undeterminable for 3 (16%), and remained positive for 8 (42%) despite resolution of symptoms. Although preliminary, these data suggest ABLC has significant activity in patients with AIDS-associated cryptococcal meningitis. Because this formulation has less hematologic and renal toxicity than does AmB, further evaluation of ABLC is warranted.

% Response per treatment group of all randomized patients and of recipients of >= 12 doses().				
	Abelcet N=8 (6)	Abelcet 9 (7)	Abelcet 21 (19)	Amphotericin B 17 (14)
Daily Dose week 1&2 mg/kg	1.2	2.5	5	0.7
Week 3-6 (3 x/week @ mg/kg)	2.5	5	5	1.2
Clinical Success	63 (83)	44 (57)	86 (95)	65 (79)
Clinical Failure	13 (17)	33 (14)	5 (5)	12 (14)
Mean Change in Scr (mg/dl) from Baseline				
Week 1	-0.14	-0.08	0.28	0.3
Week 2	-0.2	-0.18	0.34	0.68
Week 3	-0.24	-0.02	0.42	0.96
Week 4	-0.32	0.16	0.3	0.94
Week 5	-0.2	0.28	0.4	0.6
Week 6	-0.24	0.1	0.5	0.94
Severe Adverse Effects	34% (13/38)			29% (5/17)

A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B (AmBisome) versus amphotericin B lipid complex (Abelcet) in the empirical treatment of febrile neutropenia. L Amph/ABL C Collaborative Study Group. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A.

In this randomized double-blind study to compare safety of 2 lipid formulations of amphotericin B, neutropenic patients with unresolved fever after 3 days of antibacterial therapy were randomized (1:1:1) to receive amphotericin B lipid complex (ABL C) at a dose of 5 mg/kg/d (n=78), liposomal amphotericin B (L Amph) at a dose of 3 mg/kg/d (n=85), or L Amph at a dose of 5 mg/kg/d (n=81). L Amph (3 mg/kg/d and 5 mg/kg/d) had lower rates of fever (23.5% and 19.8% vs. 57.7% on day 1; P<.001), chills/rigors (18.8% and 23.5% vs. 79.5% on day 1; P<.001), nephrotoxicity (14.1% and 14.8% vs. 42.3%; P<.01), and toxicity-related discontinuations of therapy (12.9% and 12.3% vs. 32.1%; P=.004). After day 1, infusion reactions were less frequent with ABL C, but chills/rigors were still higher (21.0% and 24.3% vs. 50.7%; P<.001). Therapeutic success was similar in all 3 groups.

	AmBisome	AmBisome	Abelcet	AmBisome	AmBisome	Abelcet
	Day 1			Days 2-5		
	3 mg/kg/day n=85	5 mg/kg/day n=81	5 mg/kg/day n=78	3 mg/kg/day n=81	5 mg/kg/day n=74	5 mg/kg/day n=71
Chills/rigors	18.8%	23.5%	79.5%	21%	24.3%	50.7%
Fever > 1 C increase	23.5%	19.8%	57.7	19.8%	28.4%	45.1%
Nausea	10.6%	8.6%	11.5%	9.9%	14.9%	11.3%
Vomiting	5.9%	6.2%	14.1%	6.2%	8.1%	9.9%
Total	51.8%	48.1%	88.5%	49.4%	44.6%	66.2%
Nephrotoxicity (All Days)						
1.5 x Baseline	29.4%	25.9%	62.8%			
2 x Baseline	14.1%	14.8%	42.3%			
3 x Baseline	5.9%	6.2%	26.9%			
Successful Response	40%	42%	33.3%			
Treatment Failure	51%	47%	52%			

Leuk Lymphoma 2001 Feb;40(5-6):511-20

Comparison of amphotericin B lipid complex (ABL C) vs. ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. Fleming RV, Kantarjian HM, Husni R, Rolston K, Lim J, Raad I, Pierce S, Cortes J, Estey E. Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston 77030, USA.

Randomized open label. Fungal infections remain a major cause of treatment failure and death in acute leukemia. New liposomal preparations of amphotericin B are now available. While less toxic, their comparative efficacy and toxicity profiles are unknown. In this study the comparative efficacy and safety of ABL C (Abelcet) vs. AmBisome was evaluated in seventy-five patients with leukemia who developed 82 episodes of suspected or documented mycosis, and were treated (1:1) with either ABL C (n=43) or AmBisome (n=39). Both drugs were dosed accordingly from 3 to 5 mg/kg/day. Using an intent-to-treat analysis, the overall response to therapy was 27/43 (63%) for ABL C and 15/39 (39%) for AmBisome (p=0.03). Median dose and duration of treatment was 10 days at 3 mg/kg for ABL C and 15 days at 4 mg/kg for AmBisome. *Acute, not dose-limiting infusion side effects were seen in 70% vs. 36% (p=0.002), ABL C vs. AmBisome.* Increase of bilirubin > 1.5 times from baseline was 38% vs. 59%, ABL C vs. AmBisome (p=0.05). ABL C and AmBisome were equally effective for the treatment of suspected or documented fungal infections. While, acute infusion-toxicity was greater with ABL C, infusion toxicity requiring discontinuation was similar for both drugs. AmBisome was better tolerated than ABL C but was associated with mild abnormalities in liver function tests at the end of therapy.

AmBisome

AmBisome (Amphotericin B liposome) Data from the Package Insert (94-0-002)

A randomized, double-blind, comparative multi-center trial, evaluated the efficacy of AmBisome (1.5-6 mg/kg/day) compared with amphotericin B deoxycholate (0.3-1.2 mg/kg/day) in the empiric treatment of 687 adult and pediatric neutropenic patients who were febrile despite having received at least 96 hours of broad spectrum antibacterial therapy. Therapeutic success required: resolution of fever during the neutropenic period, absence of an emergent fungal infection, patient survival for at least 7 days post therapy, no discontinuation of therapy due to toxicity of lack of efficacy, and resolution of any study-entry fungal infection.

Empiric Therapy in Febrile Neutropenic Patients (Package Insert Data)		
	AmBisome (amphotericin B Liposome)	Amphotericin B Deoxycholate
Number of Patients Receiving at least one dose of study drug	343	344
Overall Success	49.9%	49.1%
Fever Resolution During Neutropenic period	58%	58.1%
No Treatment Emergent Fungal Infection	87.5%	87.7%
Survival through 7 days post study drug	92.7%	89.5%
Study Drug not Prematurely Discontinued Due to Toxicity of Lack of Efficacy	85.7%	81.4%
	Emergent Fungal Infections	
Mycologically confirmed fungal infection	3.2%	7.8%
Clinically diagnosed fungal infection	9.3%	4.7%
Total emergent fungal infections	12.5%	12.5%

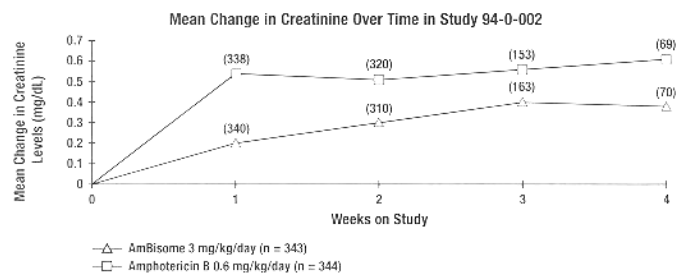
AmBisome in treatment of cryptococcal meningitis in HIV Infected Patients (Package Insert Data)

A randomized, double-blind, comparative multi-center trial, evaluated the efficacy of AmBisome compared with amphotericin B deoxycholate for treatment of cryptococcal meningitis in 267 HIV positive patients. Patients received study drug once daily for an induction period of 11 to 21 days. Following induction, all patients were switched to oral fluconazole 400 mg/day for adults and 200 mg/day for patients less than 13 years of age to complete 10 weeks of protocol directed therapy. Week two success was defined as CSF culture conversion. Week ten success was defined as clinical success at week 10 plus CSF culture conversion at or prior to week 10.

	AmBisome (amphotericin B Liposome) 3 mg/kg	AmBisome (amphotericin B Liposome) 6 mg/kg	Amphotericin B Deoxycholate 0.7 mg/kg
Success at 2 Weeks	58.3% (35/60) NS	48% (36/75) NS	47.5% (29/61) NS
Success at 10 Weeks	37% (27/73) NS	49% (42/85) NS	53% (40/76) NS
Survival Rates	86 (74/86) NS	90% (85/94) NS	89% (77/87) NS

Selected ADRs %			
Empiric Therapy in Febrile Neutropenic Patients Randomized, double blind, multi-center Study 94-0-002 NEJM 1999;340:764-71 Walsh TJ			
	Amphotericin B liposome AmBisome N=343 %	Amphotericin B Deoxycholate N=344 %	
Chills	47.5%	75.9%	
Hypertension (IR)	2.3%	11.3%	
Hypotension (IR)	3.5%	8.1%	
Tachycardia (IR)	2.3%	12.5%	
Dyspnea (IR)	4.7%	7.3%	
Creatinine $\uparrow \geq 100\%$ Over baseline	18.7%	33.7% See Graphic	
Mean Peak Creatinine mg/dl	1.24	1.52	
Mean creatinine Δ from baseline mg/dl	0.48	0.77	
BUN Increase	21%	31%	
Creatinine Increase	22.4%	42.2%	

Hypernatremia	4%	11%	
Infusion Fever <i>without pretreatment</i>	17%	44%	
Chill/rigors <i>without pretreatment</i>	18%	54%	
Study 94-0-034 Randomize, double-blind comparison in Neutropenia Wingard JR Clinical Infectious Diseases 2000;31:1155-63			
	Amphotericin B liposome AmBisome 3 mg/kg/day N=85 %	Amphotericin B liposome AmBisome 5 mg/kg/day N=81 %	Amphotericin B Lipid Complex Abelcet 5 mg/kg/day n=78 %
Chill/rigors	40%	48%	89.7%
Hypotension	10.6%	7.4%	19.2%
Serum Creatinine 1.5 x Baseline	29.4%	25.9%	62.8%
Serum Creatinine 2 x Baseline	14.1%	14.8%	42.3%
BUN Increase	20%	18.5%	28.2%
Creatinine increase	20%	18.5%	48.7%
Infusion Fever <i>without pretreatment</i>	23.5%	19.8%	57.7%
Chills/rigors <i>without pretreatment</i>	18.8%	23.5%	79.5%
Cryptococcal meningitis Therapy Study 94-0-013 Randomized double-blind multi-center			
	Amphotericin B liposome AmBisome 3 mg/kg/day n=86 %	Amphotericin B liposome AmBisome 6 mg/kg/day n=94 %	Amphotericin B Deoxycholate 0.7 mg/kg/day n=87 %
Serum Creatinine 1.5 x Baseline	35%	47%	60%
Serum Creatinine 2 x Baseline	14%	21%	33%
BUN Increase	9.3%	7.4%	10.3%
Creatinine Increase	18.6%	39.4%	43.7%
Hypokalemia	31.4%	51.1%	48.3%
Hypomagnesemia	29.1%	48.9%	40.2%
Infusion Fever (>1 degree C) <i>with pretreatment</i>	7%	9%	28%
Chills/rigors <i>with pretreatment</i>	6%	9%	48%



Mycoses 2000 Oct;43(9-10):325-32

Review of comparative studies between conventional and liposomal amphotericin B (Ambisome) in neutropenic patients with fever of unknown origin and patients with systemic mycosis. Blau IW, Fauser AA. Clinic of Bone Marrow Transplantation and Haematology/Oncology, Idar-Oberstein, Germany.

Fungal infections are an important cause of morbidity and mortality in immunocompromised patients. Treatment with amphotericin B is the main therapeutic approach. However, this treatment is limited by the substantial toxicity. We present the data of the first randomized prospective comparative trial in adults (134 patients with fever of unknown origin) with conventional amphotericin B and a liposomal formulation of amphotericin B (AmBisome, published in 1997 by Prentice et al. (Br. J. Haematol. 98, 711-718) and the data of adults with documented fungal infections (59 patients), treated in this trial. Patients received either conventional amphotericin B 1 mg kg⁻¹ per day, liposomal amphotericin B 1 mg kg⁻¹ per day or liposomal amphotericin B 3 mg kg⁻¹ per day. Patients were entered if they had fever of unknown origin (FUO), defined as temperature of 38 degrees C or more, not responding to 96 h of systemic broad-spectrum antibiotic treatment, and neutropenia (< 0.5 x 10⁹ l⁻¹). Efficacy of treatment was assessed, with success defined as resolution of fever for three consecutive days (< 38 degrees C) in the group of patients with FUO and the freedom of clinical signs and/or the elimination of fungus in the group of patients with documented fungal infections. The safety of treatment and renal and hepatic toxicity of liposomal and conventional amphotericin B were compared. No statistically significant difference was found in the treatment efficacy in the three study arms. However, there is a tendency of better treatment results in the two groups of patients, who received liposomal amphotericin B. Thirty-five per cent of patients with documented fungal infections and 46% of patients with FUO responded to amphotericin B. In the patients group, that received 1 mg kg⁻¹ liposomal amphotericin B it was 63 and 49%, in the group of patients that received 3 mg kg⁻¹ liposomal amphotericin B it was 47 and 64%. Evidence of toxicity due to amphotericin B was seen in 50 patients (83%), toxicity due to liposomal amphotericin B, 1 mg kg⁻¹, was seen in 35 patients (50%), and due to liposomal amphotericin B 3 mg kg⁻¹ in 34 patients (54%). This was a statistically significant difference (P = 0.001). It was concluded that liposomal amphotericin B was safer than conventional amphotericin B, but both formulations are equivalent in treatment efficacy. The prophylactic use of amphotericin B in these immunocompromised patients is discussed.

N Engl J Med 1999 Mar 11;340(10):764-71

Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, Pappas P, Seibel N, Greenberg RN, Dummer S, Schuster M, Holcenberg JS. Division of Clinical Sciences, National Cancer Institute, Bethesda, MD 20892, USA.

BACKGROUND: In patients with persistent fever and neutropenia, amphotericin B is administered empirically for the early treatment and prevention of clinically occult invasive fungal infections. However, breakthrough fungal infections can develop despite treatment, and amphotericin B has substantial toxicity. **METHODS:** We conducted a randomized, double-blind, multicenter trial comparing liposomal amphotericin B (3 mg/kg/day) with conventional amphotericin B (0.6 mg/kg/day) as empirical antifungal therapy in patients who continued to have fever and neutropenia after 5 days of empiric antibacterial therapy. **RESULTS:** The mean duration of therapy was 10.8 days for liposomal amphotericin B (343 patients) and 10.3 days for conventional amphotericin B (344 patients). The composite rates of successful treatment were similar (50 percent for liposomal amphotericin B and 49 percent for conventional amphotericin B) and were independent of the use of antifungal prophylaxis or colony-stimulating factors. The outcomes were similar with liposomal amphotericin B and conventional amphotericin B with respect to survival (93 percent and 90 percent, respectively), resolution of fever (58 percent and 58 percent), and discontinuation of the study drug because of toxic effects or lack of efficacy (14 percent and 19 percent). There were fewer proved breakthrough fungal infections among patients treated with liposomal amphotericin B (11 patients [3.2 percent]) than among those treated with conventional amphotericin B (27 patients [7.8 percent], P=0.009). *This data is also in the AmBisome package insert but the number are different (12.5% for each group).* With the liposomal preparation significantly fewer patients had infusion-related fever (17 percent vs. 44 percent), chills or rigors (18 percent vs. 54 percent), and other reactions, including hypotension, hypertension, and hypoxia. Nephrotoxic effects (defined by a serum creatinine level two times the upper limit of normal) were significantly less frequent among patients treated with liposomal amphotericin B (19 percent) than among those treated with conventional amphotericin B (34 percent, P<0.001). 15% of those receiving AmBisome and 27% of those receiving conventional amphotericin received reduced doses secondary to nephrotoxicity. **CONCLUSIONS:** Liposomal amphotericin B is as effective as conventional amphotericin B for empirical antifungal therapy in patients with fever and neutropenia, and it is associated with fewer breakthrough fungal infections (Not according to package insert using same study), less infusion-related toxicity, and less nephrotoxicity.

Ann Intern Med 2002 Jul 16;137(2):105-9

Safety and efficacy of liposomal amphotericin B (3 mg/kg/day) compared with conventional amphotericin B (0.7 mg/kg/day) for induction therapy of histoplasmosis in patients with AIDS (Infused over 2 hours daily for 2 weeks followed by itraconazole for 10 weeks). Johnson PC, Wheat LJ, Cloud GA, Goldman M, Lancaster D, Bamberger DM, Powderly WG, Hafner R, Kauffman CA, Dismukes WE; U.S. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Division of General Medicine, University of Texas-Houston Medical School, 6431 Fannin, MSB 1.122, Houston, TX 77030, USA. Philip.C.Johnson@uth.tmc.edu

BACKGROUND: In patients with moderate to severe histoplasmosis associated with AIDS, the preferred treatment has been the deoxycholate formulation of amphotericin B. However, serious side effects are associated with use of amphotericin B. **OBJECTIVE:** To compare amphotericin B with liposomal amphotericin B for induction therapy of moderate to severe disseminated histoplasmosis in patients with AIDS.

DESIGN: Randomized, double blind, multicenter clinical trial. **SETTING:** 21 sites of the U.S. National Institute of Allergy and Infectious Diseases Mycoses Study Group. **PATIENTS:** 81 patients with AIDS and moderate to severe disseminated histoplasmosis. **MEASUREMENTS:** Clinical success, conversion of baseline blood cultures to negative, and acute toxicities that necessitated discontinuation of treatment. **RESULTS:** Clinical success was achieved in 14 of 22 patients (64%) treated with amphotericin B compared with 45 of 51 patients (88%) receiving liposomal amphotericin B $p=0.014$ (difference, 24 percentage points [95% CI, 1 to 52 percentage points]). Fifty-five percent (55%) of patients treated with AmBisome and 32% treated with amphotericin B successfully completed therapy before 14 days. Culture conversion rates were similar. Three patients treated with amphotericin B and one treated with liposomal amphotericin B died during induction ($P = 0.04$). Overall mortality was 7.5% (4/53) AmBisome and 20.8% (5/24) amphotericin B. Infusion-related side effects were greater with amphotericin B (63%) than with liposomal amphotericin B (25%) ($P = 0.002$) (Note a 2 hour amphotericin infusion is not normally recommended). Nephrotoxicity (doubling of creatinine from baseline) occurred in 37% of patients treated with amphotericin B and 9% of patients treated with liposomal amphotericin B ($P = 0.003$). **CONCLUSION:** Liposomal amphotericin B seems to be a less toxic alternative to amphotericin B and is associated with improved survival.

Amphotec (amphotericin B Cholesteryl Sulfate complex, ABCD)

Data from 161 patients with proven or probable aspergillus infections were pooled from 5 non-comparative open label studies.

Response Rates for evaluable Patients (Amphotec Package Insert)			
Reason for use	Complete Response	Partial Response	Response Rate
Amphotericin B Deoxycholate failure*	10.7% (3/28)	32% (9/28)	42.8% (12/28)
Nephrotoxicity**	13.8% (5/36)	33.3% (12/36)	47.2% (17/36)
Preexisting renal impairment***	6.25% (1/16)	43.8% (7/16)	50% (8/16)
Total	11.1% (9/80)	35% (28/80)	46.2% (37/80)

*Based on clinical judgment after receiving a minimum of 7 days of therapy or a minimum total dose of 15 mg/kg.

** Serum creatinine that double from baseline or increased by ≥ 1.5 mg/dl or increased to ≥ 2 mg/dl.

*** Serum creatinine that increased to > 2 mg/dl due to reason other than amphotericin B deoxycholate.

- Acute infusion-related reactions with Amphotec including fever, chills, hypoxia, hypotension, nausea, or tachypnea, may occur 1-3 hours after starting infusion. These reactions are usually more severe or more frequent with the initial doses of Amphotec and diminish with subsequent doses. These reactions can be managed by pretreatment with antihistamines and corticosteroids and/or by reducing the rate of infusion.

Adverse Events (Amphotec Package Insert)		
	Amphotec N=150	Amphotericin B Deoxycholate N=146
Chills	77%	56%
Fever	55%	47%
Chills & Fever	7%	2%

Data from randomized double-blinded studies of empiric treatment of febrile neutropenic patients or treatment of first-line aspergillosis.

Randomized double blind multicenter trial in febrile neutropenia Net Mean Serum Creatinine Change (mg/dl) (number of patients) (Amphotec Package Insert)				
	Day 4	Day 7	Day 10	Day 13
Amphotericin B Deoxycholate 0.8 mg/kg/day	0.6 (88)	0.69 (71)	0.67 (47)	0.7(26)
Amphotec Amphotericin B Cholesteryl Sulfate Complex 4 mg/kg/day	0.25(93)	0.29 (78)	0.38 (58)	0.32 (34)

*Base line creatinine ≤ 1.5 md/dl, Amphotericin B Deoxycholate 0.77 mg/dl, Amphotec 0.8 mg/dl

Two randomized controlled trial found in literature, noted below.

Clin Infect Dis 2002 Aug 15;35(4):359-66

A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion (Amphotec) versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M, van Burik JA, Laverdiere M, Safrin S, Wingard JR. Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

We report a randomized, double-blind, multicenter trial in which amphotericin B colloidal dispersion (ABCD [Amphotec]; 6 mg/kg/day) was compared with amphotericin B (AmB; 1.0-1.5 mg/kg/day) for the treatment of invasive aspergillosis in 174 patients. For evaluable patients in the ABCD and AmB treatment groups, respective rates of therapeutic response (52% vs. 51%; P=1.0), mortality (36% vs. 45%; P=.4), and death due to fungal infection (32% vs. 26%; P=.7) were similar. Renal toxicity was lower (25% vs. 49%; P=.002) and the median time to onset of nephrotoxicity was longer (301 vs. 22 days; P<.001) in patients treated with ABCD. Rates of drug-related toxicity in patients receiving ABCD and AmB, respectively, were 53% versus 30% (chills), 27% versus 16% (fever), 1% versus 4% (hypoxia) and 22% versus 24% (toxicity requiring study drug discontinuation). ABCD appears to have equivalent efficacy and superior renal safety, compared with AmB, in the treatment of invasive aspergillosis. However, infusion-related chills and fever occurred more frequently in patients receiving ABCD than in those receiving AmB.

Clin Infect Dis 1998 Aug;27(2):296-302

Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. White MH, Bowden RA, Sandler ES, Graham ML, Noskin GA, Wingard JR, Goldman M, van Burik JA, McCabe A, Lin JS, Gurwith M, Miller CB. Infectious Disease Service, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.

We conducted a prospective, randomized, double-blind study comparing amphotericin B colloidal dispersion (ABCD) with amphotericin B in the empirical treatment of fever and neutropenia. Patients with neutropenia and unresolved fever after > or = 3 days of empirical antibiotic therapy were stratified by age and concomitant use of cyclosporine or tacrolimus. Patients were then randomized to receive therapy with ABCD (4 mg/kg/day) or amphotericin B (0.8 mg/kg/day) for < or = 14 days. A total of 213 patients were enrolled, of whom 196 were evaluable for efficacy. Fifty percent of ABCD-treated patients and 43.2% of amphotericin B-treated patients had a therapeutic response (P = 0.31). Renal dysfunction was less likely to develop and occurred later in ABCD recipients than in amphotericin B recipients (P < .001 for both parameters). Infusion-related hypoxia and chills were more common in ABCD recipients than in amphotericin B recipients (P = .013 and P = .018, respectively). ABCD appeared comparable in efficacy with amphotericin B, and renal dysfunction associated with ABCD was significantly less than that associated with amphotericin B. However, infusion-related events were more common with ABCD treatment than with amphotericin B treatment.

	Amphotec N=102	Amphotericin N=99
Overall response	50%	43.2%
Documented or suspected fungal infection during study drug administration or within 7 days of study drug discontinuation	14.3%	14.7%
Documented fungal infection	3.1%	3.2%
Defervescence	53.5%	57.9%
Median # of days to defervescence	7	5
Sustained defervescence	33.7%	40%
Nephrotoxicity (doubling of creatinine or 50% decline in creatinine clearance)	20.4%	53.7% P < 0.001
Time to 50% with nephrotoxicity	Never achieved	7 Days
Chills	79.8%	65.4%
Hypoxia*	13.7% (13/102)	3.3% (3/99) p=0.013
Mortality through day 28	15.7% (16/102)	13.1% (13/99)

Note 50% of patients in both groups were receiving either tacrolimus or cyclosporin

* Most hypoxic episodes (11 ABCD, 3 amphotericin) were temporally associated with rigors and fever and required treatment with supplemental oxygen and other medications. All episodes resolved, but one amphotericin B and five ABCD recipients were withdrawn from the study as a result.

Clin Infect Dis 1997 Apr;24(4):635-42

Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis. White MH, Anaissie EJ, Kusne S, Wingard JR, Hiemenz JW, Cantor A, Gurwith M, Du Mond C, Mamelok RD, Bowden RA. Memorial Sloan Kettering Cancer Center, New York, New York 10021, USA.

To assess the efficacy and safety of amphotericin B colloidal dispersion (ABCD), 82 patients with proven or probable aspergillosis who were treated in 5 open label clinical trials with ABCD were compared retrospectively with 261 patients with aspergillosis who were treated with amphotericin B at six cancer or transplant centers from January 1990 to June 1994. The groups were balanced in terms of underlying disease; ABCD recipients were younger and more likely to have preexisting renal insufficiency than were amphotericin B recipients (40.7% vs. 8.7%, respectively), and amphotericin B recipients were more likely to be neutropenic at baseline than were ABCD recipients (42.5% vs. 15.9%, respectively). Response rates (48.8%) and survival rates (50%) among ABCD-treated patients were higher than those (23.4% and 28.4%, respectively) among amphotericin B-treated patients (P < .001 for both comparisons). Renal dysfunction developed less frequently in ABCD recipients than in amphotericin B recipients (8.2% vs. 43.1%, respectively; P < .001). Multivariate analysis revealed that treatment group was the best predictor of response, mortality, and nephrotoxicity (ABCD: relative risk [RR] = 3.00, P = .002; RR = 0.35, P < .001; and RR = 0.13, P = .001; respectively). This retrospective study suggests that in the treatment of aspergillosis ABCD causes fewer nephrotoxic effects than amphotericin B and the efficacy of ABCD is at least comparable with that of amphotericin B.

					Low Dose	High Dose
Drug	mg	Cost/Dose	Dose mg/kg/day	Dose mg/kg/day	Cost per day for 80 kg	Cost per day for 80 kg
Amphotericin B Deoxycholate (Fungizone)	50	\$6.13	1.0	1.5	\$12.26	\$18.39
Amphotericin B Cholesteryl Sulfate Complex (Amphotec)	50	\$46.06	3.0	4.0	\$230.30	\$322.42
Amphotericin B Cholesteryl Sulfate Complex (Amphotec)	100	\$78.40	3.0	4.0	\$235.20	\$313.60
Amphotericin B Liposome (Ambisome)	50	\$153.37	3.0	5.0	\$766.85	\$1,226.96
Amphotericin B Lipid Complex (Abelcet)	50	\$98.98	5.0	5.0	\$791.84	\$791.84
Amphotericin B Lipid Complex (Abelcet)	100	\$156.80	5.0	5.0	\$627.20	\$627.20
Caspofungin Acetate (Cancidas)	70	\$352.67	70 x1	50 qd	\$352.67	\$273.77
Caspofungin Acetate (Cancidas)	50	\$273.77	50 qd	70 qd	\$273.77	\$352.67
Itraconazole (Sporanox capsule)	100	\$6.53	200 mg TID x 3 days	200 qd	\$39.18	\$13.06
Itraconazole (Sporanox)	250	\$149.47	200 mg q12h x 4	200 qd	\$298.94	\$149.47
Voriconazole (VFEND)	200	\$83.30	6 mg/kg q12h x2	4 mg/kg q12h	\$499.80	\$333.20
Voriconazole (VFEND tablet)	200	\$24.50	200 mg bid	300 mg bid	\$49.00	\$73.50
Voriconazole (VFEND tablet)	50	\$6.13	100 mg bid	150 mg bid	\$24.50	\$36.75

