



Pharmacy

March/April 1998

Update

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information
Service, and Endocrinology Clinical
Pharmacy Specialist
kcalis@nih.gov

Associate Editor
Amy M. Heck, Pharm.D.
Specialized Resident in Drug
Information Practice and
Pharmacotherapy
aheck@nih.gov

In This Issue

- **Amphotericin B Formulations**
- **Intravenous (I.V.) Amphotericin B Administration Guidelines (Table 1)**
- **Susceptibility of Common NIH Microorganisms**
- **Formulary Update**

Amphotericin B Formulations

Amphotericin B remains the drug of choice for many fungal infections. However, intravenous administration of amphotericin B deoxycholate is often complicated by both infusion-related adverse reactions (e.g., fever, chills, rigors, nausea, vomiting, hypotension, and rarely hypertension) and systemic toxicities (e.g., nephrotoxicity, acidosis, hypokalemia, hypomagnesemia, and anemia). Symptomatic support with medications such as antipyretics and antihistamines can often ease the discomfort associated with infusion-related reactions. The incidence and severity of nephrotoxicity associated with the amphotericin B deoxycholate preparation can be minimized by adequate saline hydration in patients who can tolerate increased fluid intake. Amphotericin B administration guidelines were recently developed by the Antimicrobials Subcommittee and were approved by the Pharmacy and Therapeutics (P&T) Committee (see Table 1).

Several lipid formulations of amphotericin B have recently been approved for use in the United States. These formulations appear to be less nephrotoxic than conventional amphotericin B, but the cost of therapy is significantly higher (see Table 2). In patients in whom conventional amphotericin B therapy is contraindicated or not well tolerated, the newer products are encouraging alternatives. However, there are few studies that directly compare the relative safety and efficacy of these new lipid products.

Two lipid formulations of amphotericin B were recently approved by the P&T Committee for use at the NIH Clinical Center: Abelcet® (amphotericin B lipid complex, ABLC) and AmBisome® (liposomal amphotericin B). Use of these agents requires approval from the NIAID or NCI Infectious Diseases Services.

Upon recommending approval of these amphotericin B lipid formulations, the P&T Committee issued the following statements:

- ❖ Current data suggest that lipid formulations of amphotericin B are effective but less toxic in comparison to conventional amphotericin B.
- ❖ To date, there are no comparative data by which to evaluate the relative efficacy, safety, and tolerability of the various lipid formulations of amphotericin B (compared to other lipid formulations).
- ❖ Lipid formulations of amphotericin B are substantially more expensive than conventional amphotericin B.
- ❖ Conventional amphotericin B is indicated as initial therapy for the treatment of invasive fungal infections.
- ❖ Both Abelcet® and AmBisome® are indicated as second-line therapy for treatment of invasive fungal infections in patients who are intolerant of or refractory to conventional antifungal therapy.
- ❖ Both conventional amphotericin B and AmBisome® are indicated as initial empirical antifungal therapy for neutropenic patients with persistent fever who are unresponsive to broad-spectrum antibiotics.
- ❖ Pharmacoeconomic studies are currently under way to clarify the role of lipid formulations of amphotericin B in the management of invasive fungal infections.

Table 1. Clinical Center Amphotericin B Deoxycholate Administration Guidelines**Indications**

- First-line therapy for most systemic mycoses, especially in immunocompromised hosts
- Empiric therapy in febrile neutropenic patients unresponsive to antibacterial therapy
- Oropharyngeal or esophageal candidiasis refractory to topical antifungals and oral azole therapy

Adverse Reactions**Infusion Related:**

- Fever, chills, rigors, and hypotension; rarely hypertension, nausea, vomiting, and anorexia
- Thrombophlebitis (if given through a peripheral line)

Non-Infusion Related:

- Nephrotoxicity (azotemia and renal tubular acidosis are dose and duration dependent)
- Renal electrolyte wasting (K^+ , Mg^{++} , and HCO_3^-)
- Normochromic, normocytic anemia

Suggested Dosages for Selected Systemic Mycoses

- | | |
|----------------------|--------------------------------------------------------------|
| • Aspergillosis | 1.0 - 1.5 mg/kg/day |
| • Blastomycosis | 0.4 - 0.6 mg/kg/day |
| • Candidiasis | 0.3 - 1.0 mg/kg/day (oroesophageal) |
| | 0.5 - 1.0 mg/kg/day (other sites) |
| • Coccidioidomycosis | 0.5 - 1.0 mg/kg/day |
| • Cryptococcosis | 0.5 - 1.0 mg/kg/day (may use with flucytosine 100 mg/kg/day) |
| • Fusariosis | 1.0 - 1.5 mg/kg/day |
| • Histoplasmosis | 0.5 - 0.7 mg/kg/day |
| • Mucormycosis | 0.5 - 1.5 mg/kg/day |

Administration**Test dose:**

- Not necessary

Dose Escalation (over 2-3 days):

- Not necessary; may reduce infusion-related adverse effects during the first few days
- Not recommended for patients with serious or life-threatening infections

Infusion Solution:

- Always dilute in dextrose 5% in water (incompatible with solutions containing sodium chloride)
- Final concentrations:
 - ≤ 0.1 mg/ml if infused through a peripheral line
 - ≤ 1.4 mg/ml if infused through a central line

Infusion Rate:

- Over 2 - 4 hours

Note: use of in-line filter is not recommended

Monitoring During Infusion

- Vital signs every 30 minutes during the first dose, then every 1-2 hours with subsequent doses
- Monitor for infusion-related symptoms throughout administration period
- Review signs and symptoms of infusion-related reactions with patient before administration of first dose

Management of Infusion-Related Reactions**For immediate response in managing rigors:**

- Meperidine given by slow I.V. injection over at least 5 minutes
 - Adults: 25-50 mg
 - Children: 1-1.5 mg/kg

Fever:

- Adults: acetaminophen 500-1000 mg p.o. or 650 mg suppository
- Children: dose according to weight and age

Pre-Medication (after previous infusion-related reaction):

- Acetaminophen 650 mg p.o. (or suppository) with or without diphenhydramine (25-50 mg p.o. or I.V. or 0.75-1.25 mg/kg p.o. or I.V. in pediatric patients) 30 minutes prior to start of infusion

If symptoms persist despite pre-medication:

- Hydrocortisone 25-50 mg (10-25 mg in pediatric patients) prior to infusion or added to amphotericin B solution

For preventing thrombophlebitis and infusion-site discomfort when peripheral line is used:

- Heparin 100-500 units added to amphotericin B solution

Prevention of Nephrotoxicity**Saline Hydration or Sodium Loading (3-6 mEq of Na^+ /kg):**

- Hydration with one liter of 0.9% NaCl solution prior to amphotericin B infusion may reduce incidence and/or severity of nephrotoxicity
- For patients with prolonged therapy, continuous hydration for up to one week after therapy may be necessary
- Alternatively, continuous I.V. or oral hydration can be used throughout the day (with equivalent amounts of sodium)
- Saline hydration should be given with caution to patients with cardiac compromise and to those who develop hypertension during amphotericin B infusion
- Saline hydration should not be given to patients with end-stage renal disease

Management of K^+ , Mg^{++} , and HCO_3^- Loss

- K^+ , Mg^{++} , and HCO_3^- renal wasting usually becomes apparent during the first week of therapy and continues throughout treatment course; aggressive replacement is necessary
- Intravenous potassium (acetate or chloride), and magnesium sulfate can be added to hydration fluid
- Oral supplementation can be given if tolerated
- Electrolytes and renal function should be monitored after completion of therapy
- Continued hydration or electrolyte supplementation may be necessary in some cases

Percent Susceptibility of Common NIH Microorganisms

	Concentration (µg/ml)	Ps. aeruginosa - CF "(61) a,e"	Ps. aeruginosa Non-CF "(105) a,f"	Stenotrophomonas maltophilia (33) b	Staphylococcus aureus (221) a	Staphylococcus epidermidis (214) a	Enterococcus faecalis (131) a	Enterococcus faecium (26) b
Amikacin	16	68	89	9	99	100	-	-
Ampicillin	8	- d	-	-	-	-	98	35
Amox./clavulan.	4/2	-	-	-	91	34	-	-
Aztreonam	8	72	65	-	-	-	-	-
Cefazolin	8	-	-	-	91	34	-	-
Cefoxitin	8	-	-	-	-	-	-	-
Ceftazidime	8	84	79	48	-	-	-	-
Ceftroxone	8	-	-	-	91	33	-	-
Ciprofloxacin	1	57	86	33	90	55	76	15
Clindamycin	2	-	-	-	92	60	-	-
Erythromycin	0.5	-	-	-	70	29	-	-
Gentamicin	4	54	75	-	93	70	-	-
Imipenem	4	74	85	-	91	33	99	38
Oxacillin	2	-	-	-	91	34	-	-
Penicillin	0.12	-	-	-	10	12	-	-
Piperacillin	64	88	88	26	-	-	-	-
Rifampin	1	-	-	-	98	87	-	-
Tobramycin	4	87	96	-	-	-	-	-
Trimeth./sulfa.	2/38	-	-	91	92	65	-	-
Vancomycin	4	-	-	-	100	100	95	65
Gent./Pen. syn.	500	-	-	-	-	-	96	69
Nitrofurantoin *	32	-	-	-	-	-	100	60

Clinical Center, National Institutes of Health, Rev. 6/97

	Concentration (µg/ml)	Escherichia coli (191) a	Klebsiella pneumoniae (97) a	Enterobacter cloacae (46) b	Citrobacter freundii (18) b	Serratia marcescens (35) b	Acinetobacter baumannii (35) c
Amikacin	16	100	98	100	100	100	97
Ampicillin	8	60	-	-	-	-	-
Amox./clavulan.	8/4	91	98	-	-	-	-
Aztreonam	8	97	93	91	89	94	-
Cefazolin	8	86	94	-	-	-	-
Cefoxitin	8	95	96	-	-	-	-
Ceftazidime	8	97	94	96	83	94	89
Ceftroxone	8	97	94	87	78	100	71
Cefuroxime	8	95	90	-	-	-	-
Ciprofloxacin	1	98	96	93	94	94	83
Gentamicin	4	94	96	93	100	100	91
Imipenem	4	100	99	96	100	100	100
Piperacillin	16	64	63	87	83	100	83
Tobramycin	4	95	96	93	100	100	89
Trimeth./sulfa.	2/38	81	95	91	59	100	80
Nitrofurantoin *	32	99	65	-	100	-	-
Sulfamethox. *	256	64	70	100	44	-	-
Tetracycline *	4	73	90	96	67	-	-

Data from C isolates. Number in parentheses is number of isolates tested.

a. January 1, 1996 through December 31, 1996.

b. January 1, 1996 through May 31, 1997.

c. January 1, 1994 through May 31, 1997.

d. Dashes indicate antibiotics not recommended for use against given organism.

e. Pseudomonas aeruginosa isolates from cystic fibrosis patients.

f. Pseudomonas aeruginosa isolates from non-cystic fibrosis patients.

* For treatment of urinary tract infections only; data are for levels achievable in urine only.

Table 2. Comparison of Amphotericin B Products

Product	Amphotericin B deoxycholate (Fungizone®) <i>Bristol-Myers Squibb</i>	Liposomal amphotericin B (AmBisome®) <i>Nexstar/Fujisawa</i>	Amphotericin B lipid complex (Abelcet®) <i>Liposome Co.</i>	Amphotericin B colloidal dispersion (Amphotec®) <i>Sequus</i>
Composition	deoxycholate	hydrogenated soy, phosphatidylcholine, cholesterol, diastearoyl phosphatidylglycerol	dimyristoyl phosphatidylcholine, dimyristoyl phosphatidylglycerol	cholesteryl sulfate
Mol % Ampho B	34%	10%	50%	50%
Diameter	< 400 nm	80 nm	1600-11,000 nm	122 nm
Structure	micelles	spherical	lipid ribbon	lipid disc
Usual Dose	1 mg/kg/day	5 mg/kg/day	5 mg/kg/day	5 mg/kg/day
Daily Cost*	\$6.00	\$826.00	\$281.00	\$252.00

*Cost based on Federal Supply Schedule for a 70-kg patient

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions:

- ❖ Tiagabine (Gabatril®), an antiepileptic agent
- ❖ Terbinafine (Lamisil®), an oral antifungal agent for the treatment of onychomycosis
- ❖ Amphotericin B lipid complex (Abelcet®), with use restricted to the Infectious Diseases Services
- ❖ Liposomal amphotericin B (AmBisome®), with use restricted to the Infectious Diseases Services
- ❖ Valacyclovir (Valtrex®), an antiviral agent
- ❖ Amiodarone injection 50 mg/mL
- ❖ Diazepam rectal gel

Editor's Note

We wish to thank Alice Pau, Pharm.D. (Table 1) and Stacey Henning, R.Ph. (Table 2) for their contributions to this issue of *Pharmacy Update*.



Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196